BJA

British Journal of Anaesthesia, 135 (1): 188–196 (2025)

doi: 10.1016/j.bja.2025.03.018
Advance Access Publication Date: 14 May 2025
Clinical Investigation

RESPIRATION AND THE AIRWAY

Multimodal prehabilitation before lung resection surgery: a multicentre randomised controlled trial

Kristian Brat[1,2,3], Milan Sova[4,5], Pavel Homolka[2,6], Marek Plutinsky[1,2], Samuel Genzor[4,5], Alena Pokorna[2,6], Filip Dosbaba[2,7], Barbora Imrichova[5,8], Zdenek Chovanec[2,9], Ladislav Mitas[2,10], Monika Mikulaskova[5,8], Michal Svoboda[2,11], Lyle Olson[12], Ivan Cundrle[2,13,*] on behalf of the study group[†] (supplement)

[1]Department of Respiratory Diseases, University Hospital Brno, Brno, Czech Republic, [2]Faculty of Medicine, Masaryk University, Brno, Czech Republic, [3]Center for Pulmonology and Interventional Bronchology, Masaryk Memorial Cancer Institute, Brno, Czech Republic, [4]Department of Pulmonary Diseases and Tuberculosis, University Hospital Olomouc, Olomouc, Czech Republic, [5]Faculty of Medicine, Palacky University Olomouc, Olomouc, Czech Republic, [6]Department of Sports Medicine and Rehabilitation, St. Anne's University Hospital Brno, Brno, Czech Republic, [7]Department of Rehabilitation, University Hospital Brno, Brno, Czech Republic, [8]Department of Sports Medicine and Cardiovascular Rehabilitation, University Hospital Olomouc, Olomouc, Czech Republic, [9]First Department of Surgery, St. Anne's University Hospital Brno, Brno, Czech Republic, [10]Department of Surgery, University Hospital Brno, Brno, Czech Republic, [11]Institute of Biostatistics and Analyses, Ltd., Brno, Czech Republic, [12]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA and [13]Department of Anesthesiology and Intensive Care, St. Anne's University Hospital Brno, Brno, Czech Republic

*Corresponding author. E-mail: Ivan.Cundrle@seznam.cz
[†]See supplementary material for a list of the study group.

Abstract

Background: Respiratory muscle training may improve ventilatory efficiency (V_E/VCO_2 slope), a strong predictor of postoperative pulmonary complications. We hypothesised that multimodal prehabilitation, incorporating high-intensity respiratory muscle training, before lung resection would reduce postoperative complications and length of hospital stay.
Methods: We conducted a prospective multicentre, randomised controlled trial (NCT04826575) to examine the effect of prehabilitation in individuals undergoing lung resection. Participants were defined as high-risk for postoperative pulmonary complications if they achieved V_E/VCO_2 slope $\geq$33, as determined by cardiopulmonary exercise testing. Participants were then randomised to either usual care or multimodal prehabilitation, which consisted of a 14-day programme of high-intensity respiratory muscle training, smoking cessation, nutritional support, and psychological support. The primary outcome were postoperative pulmonary and cardiovascular complications (pneumonia, atelectasis, respiratory failure necessitating mechanical ventilation, adult respiratory distress syndrome, prolonged air leak).
Results: A total of 122 patients (46% female; age range: 64–75 yr) completed the study. Postoperative pulmonary complications occurred in 20/58 (34%) of patients randomised to multimodal prehabilitation, compared with 35/64 (55%) patients receiving usual care (odds ratio 2.29 [95% confidence interval 1.10–4.77]; P=0.029). Hospital length of stay was shorter after multimodal rehabilitation compared with patients randomised to receive usual care (from 9 [7–11] days to 7 [6–9] days; P=0.038). After prehabilitation, mean (SD) V_E/VCO_2 slope decreased from 39 (8) to 36 (9); P=0.01. Prehabilitation also improved patient-reported quality of life measures.
Conclusions: In high-risk patients undergoing elective lung resection surgery, multimodal prehabilitation, including high-intensity respiratory muscle training to target V_E/VCO_2, reduced postoperative pulmonary complications and hospital length of stay.

Received: 23 December 2024; **Accepted:** 25 March 2025

Keywords: cardiopulmonary exercise testing; lung resection surgery; postoperative complications; prehabilitation; ventilatory efficiency

Editor's key points

- Poor ventilatory efficiency (V_E/VCO_2) is strongly associated with pulmonary complications after lung resection.
- Respiratory muscle training might improve ventilatory efficiency.
- This RCT randomised 122 patients undergoing lung resection with high V_E/VCO_2 to either usual care or multimodal prehabilitation.
- Multimodal prehabilitation reduced V_E/VCO_2, which was associated with fewer pulmonary complications.
- In high-risk patients, targeted multimodal prehabilitation using high-intensity respiratory muscle training can improve outcomes.

Lung resection surgery is the major curative opportunity for lung cancer,[1] but up to 37% of affected patients are considered inoperable owing to impaired lung function,[2] an unacceptably high risk for major postoperative (pulmonary) complications (PPCs) including death, or both.[3]

Prehabilitation is a multidisciplinary approach which may improve functional capacity (cardiopulmonary functional reserve), nutritional status, and psychological status before surgery.[4] In lung resection, studies examining the potential benefits of prehabilitation, which have primarily focused on improvement of exercise capacity, have provided conflicting results.[5–9] A large RCT showed that physical training improved aerobic performance but did not reduce early postoperative complications after lung resection.[9] These inconsistent findings may be attributable to study design, patient selection, and the intensity and duration of prehabilitation programmes.[1]

Prior studies have focussed on improving exercise capacity as assessed by peak oxygen consumption (VO_2),[8,9] which is a poor predictor of PPC.[10–14] Although ventilatory efficiency defined by the slope of minute ventilation to carbon dioxide output ratio (V_E/VCO_2 slope) has shown a stronger association with developing PPCs,[10,13,15] prehabilitation programmes based mainly on aerobic training did not improve V_E/VCO_2 slope.[16] Because respiratory muscle strength reflects V_E/VCO_2,[17] respiratory muscle training may improve V_E/VCO_2 slope. Indeed, intensive respiratory muscle strength training in patients at higher risk of PPC appears to be beneficial in cardiac surgery.[18]

We hypothesised that prehabilitation (incorporating high-intensity respiratory muscle training) would be associated with fewer postoperative complications (primary endpoint) and other complications leading to a shorter hospital length of stay in individuals undergoing elective lung resection candidates.

Methods

Study design

This was a prospective multicentre RCT conducted in three centres in the Czech Republic (St. Anne's University Hospital Brno, University Hospital Brno, and University Hospital Olomouc) between June 2021 and June 2024. The study was registered at clinicaltrials.gov (NCT04826575) and approved by the local ethics committees of St. Anne's University Hospital Brno (03G/2021), University Hospital Brno (14-100620/EK), and University Hospital Olomouc (114/20). The study was conducted in accordance with the Declaration of Helsinki, and each participant provided written informed consent.

Inclusion criteria

Inclusion criteria were planned lung resection surgery owing to lung infiltration (confirmed or highly suspicious lung tumour), age >18 yr, the ability to undergo cardiopulmonary exercise testing (CPET), and preoperative $V_E/VCO_2 \geq 33$. The V_E/VCO_2 cut-off was chosen based on the results of a previous large multicentre study showing $V_E/VCO_2 \geq 33$ to be the best cut-off to predict PPC.[13]

Exclusion criteria

Exclusion criteria were inoperability, defined as peak predicted postoperative VO_2 <10 ml kg^{-1} min^{-1} or <35% predicted (on first CPET, or on second CPET in the prehabilitation group), in association with predicted postoperative forced expiratory volume in 1 s (FEV_1) <30% and the diffusing capacity of the lung for carbon monoxide (DL_{CO}) <30%, as determined by published European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) guidelines.[19]

Screening using preoperative cardiopulmonary exercise testing

Patients who had preoperative $V_E/VCO_2 \geq 33$ were classified as high-risk for development of PPCs[13] and were randomly assigned to one of two groups: (1) prehabilitation or (2) usual care.

Cardiopulmonary exercise testing

Before surgery, all patients underwent symptom-limited CPET. The second CPET was performed only in patients who were randomised to the prehabilitation group immediately after the completion of the prehabilitation programme. CPET was conducted in accordance with the methodology outlined in our previous study.[13] In brief, electronically braked cycle ergometry (Ergoline, Ergometrics 800, Bitz, Germany) with a 12-channel electrocardiography unit (Schiller AG, AT-104, Baar, Switzerland) and linearly increasing (15 W min^{-1}) ramp protocol were used. Expired gases and volumes were analysed using the PowerCube-Ergo cardiopulmonary exercise system (Ganshorn Medizin Electronic GmbH, Niederlauer, Germany). The variables measured were peak VO_2, carbon dioxide output (VCO_2), partial pressure of end-tidal carbon dioxide (P_{ETCO_2}), tidal volume (V_T), and minute ventilation (V_E). Derived measurements consisted of the respiratory exchange ratio, dead space to tidal volume ratio (V_D/V_T), and the ventilatory efficiency slope (V_E/VCO_2 slope).

Pulmonary function tests

On the same day as the first CPET, all patients underwent pulmonary function test (PFT). Patients in the prehabilitation group underwent a second PFT upon completion of the training programme. Spirometry and DL_{CO} were included. The parameters that were selected for further evaluation were forced vital capacity, FEV_1, and DL_{CO}, in accordance with the American Thoracic Society standards.[20]

Clinical care

Patients randomised to the usual care group underwent planned lung resection surgery without delay. Anaesthesia induction and maintenance followed local protocols of each centre, with patients undergoing thoracotomy receiving a thoracic epidural catheter. All subjects were intubated with double-lumen endobronchial tubes under bronchoscopy control. During surgery, protective ventilation with a tidal volume of 4–6 ml kg^{-1} (predicted body weight) and fluid therapy of 4 ml kg^{-1} h^{-1} of crystalloid infusion were used. Postoperative care did not differ between groups. Patients in both groups underwent standard postoperative chest physiotherapy, including airway clearance techniques and early mobilisation on a daily basis with the help of a physiotherapist.

Prehabilitation intervention

The prehabilitation programme was undertaken for 14 days (immediately before planned surgery) and included (1) high-intensity inspiratory and expiratory muscle training, (2) psychological support, (3) smoking cessation, and (4) nutritional support.

High-intensity inspiratory and expiratory muscle training

A hand-held electronic transducer (Micro RPM®; Micro-Medical/CareFusion, Kent, UK) was used to measure maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). Inspiratory muscle training was done with the Threshold IMT® (Philips Respironics, Inc., Murrysville, PA, USA). Depending on the initial MEP, expiratory muscle training was done using the Threshold PEP® (Philips Respironics, Inc.) or EMST 150™ (Aspire Products, LLC, Atlanta, GA, USA).

Before training began, each patient was instructed in use of the breathing training devices. For 2 weeks, patients were instructed to train 20 min in the morning and 20 min in the afternoon (10 min inspiratory muscle training and 10 min expiratory muscle training). Patients also completed six physiotherapist-supervised sessions in the hospital (three in the first and three in the second week). The training had two phases; phase 1 (first week) training load was set on 50% of initial MIP/MEP for the entire phase. During phase 2 (second week) MIP/MEP was measured before each of the three supervised training sessions, and a new training load was set at 60% (for more details, see Supplementary material).

Psychological support

The physiotherapist instructed patients randomised to the prehabilitation group in breathing relaxation techniques as

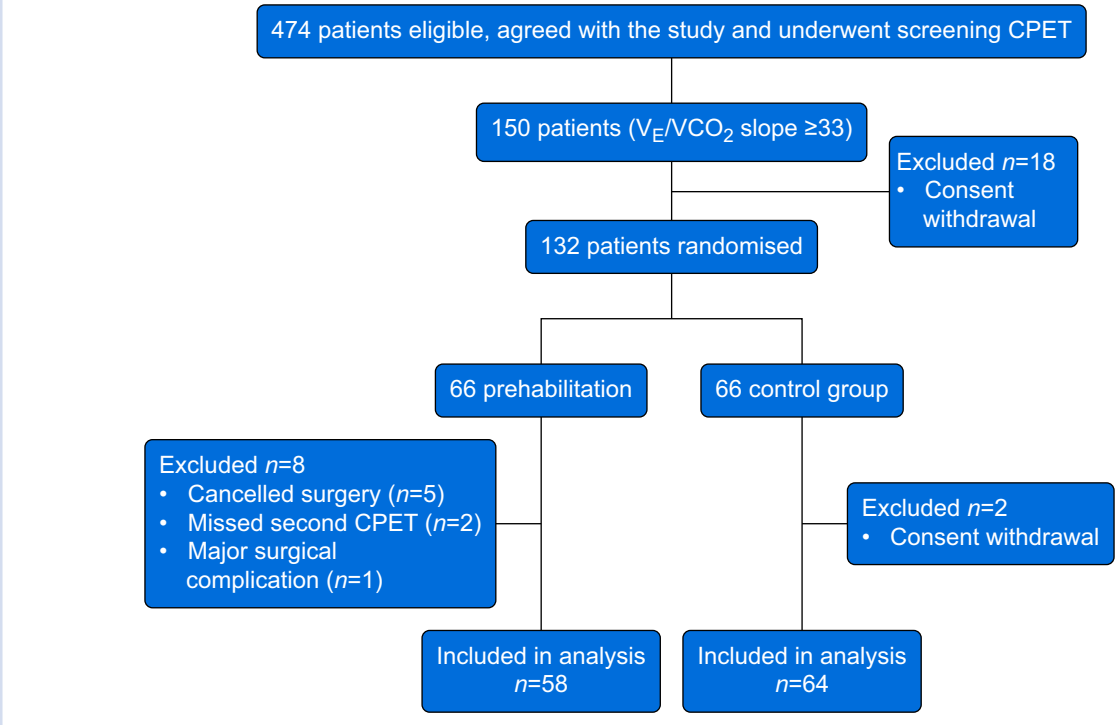

Fig 1. Study flow chart. CPET, cardiopulmonary exercise testing; V_E/VCO_2, ventilatory efficiency.

part of an intensive respiratory muscle training program. To assess the impact of the prehabilitation programme on the psychological status and quality of life, the quality of life questionnaire EQ-5D-3L was utilised.[21]

Smoking cessation

Patients who were assigned to the prehabilitation group were advised to discontinue smoking. Participation in the local smoking cessation programme was provided for those who expressed interest. The Fagerström Test of Nicotine Dependence[22] was done before and after the programme to evaluate efficacy.

Nutritional support

The Malnutrition Universal Screening Tool (MUST) score was determined for all patients in the prehabilitation group. Patients with a MUST score ≥2 were referred to the nutritional support team.

Primary outcome were both pulmonary and cardiovascular complications

Pulmonary complications were assessed during the first 30 postoperative days defined in accordance with previous studies,[1,23,24] using a composite outcome incorporating pneumonia, atelectasis, respiratory failure necessitating mechanical ventilation, adult respiratory distress syndrome, and prolonged air leak (Supplementary methods).[25]

Secondary outcomes

We recorded the following secondary outcomes: (1) duration of chest drain use; (2) hospital and ICU length of stay; (3) mortality within 30 days of surgery; and (4) cardiovascular complications were recorded as previously recommended[26] during the initial 30 postoperative days or during the hospital stay as a composite (Supplementary methods).

Randomisation and blinding

A randomization list was generated using R version 4.0.5 (R Core Team, 2021). Block randomisation was stratified according to centre, thoracotomy/video-assisted thoracoscopic surgery (VATS), and lobectomy/atypical resection. Researchers who assessed the postoperative complications were blinded to the randomisation results.

Statistics

The Shapiro–Wilk test was used to evaluate normality. Comparisons between control and prehabilitation groups were done using the unpaired *t*-test and Mann–Whitney *U*-test. Comparison of pre–post prehabilitation was done using paired *t*-test and Wilcoxon test. One-way analysis of variance (ANOVA) with Tukey's *post hoc* test and Friedman's ANOVA with *post hoc* Wilcoxon test were used to compare mean MIP/MEP and EQ-5D-3L, respectively. Differences in proportions were tested by the two-tailed Fisher's exact test. Univariate logistic regression was used to assess which of the prehabilitation parameters were associated with PPC development. Subsequently, a multivariate stepwise logistic regression model adjusted for age, sex, BMI, and Surgical Mortality Probability Model score (S-MPM)[27] was constructed to analyse which parameters were independently associated with the development of PPC. Data were summarised as mean (standard deviation; SD); $P<0.05$ was considered statistically significant. Statistical software 12.0 (StatSoft Inc., Prague, Czech Republic) and SPSS Statistics 25.0 (IBM Corp, Armonk, NY, USA) were used for statistical analysis.

Table 1 Study participants. Data are presented as *n* (%) or mean (range). COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; EQ-5D-3L, EuroQol questionnaire; f_b, breathing frequency; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; RER, respiratory exchange ratio; S-MPM, Surgical Mortality Probability Model; VCO_2, carbon dioxide output; V_D, dead space volume; V_E, minute ventilation; V_E/VCO_2, ventilatory efficiency; VO_2, oxygen consumption; V_T, tidal volume.

Parameter	Usual care (*n*=64)	Prehabilitation (*n*=58)
Age (yr)	72 (68–75)	69 (64–73)
Male	39 (61)	27 (47)
BMI (kg m^{-2})	27 (24–30)	27 (23–32)
S-MPM	5 (4–6)	5 (4–6)
COPD	23 (36)	28 (48)
EQ-5D-3L (mm)	65 (50–80)	60 (50–75)
Pulmonary function tests		
FEV_1 (%)	88 (17)	82 (18)
FVC (%)	97 (16)	93 (18)
DL_{CO} (%)	82 (23)	75 (24)
CPET peak exercise		
VO_2 (ml kg^{-1} min^{-1})	15.8 (13.9–17.6)	15.2 (13.2–18.4)
VCO_2 (L min^{-1})	1.36 (1.15–1.74)	1.3 (1.2–1.7)
RER	1.13 (1.06–1.24)	1.13 (1.05–1.24)
V_E (L min^{-1})	60 (47–68)	56 (47–68)
V_T (L)	1.7 (1.3–2.0)	1.5 (1.2–1.9)
f_b (bpm)	36 (8)	38 (7)
V_D/V_T	0.21 (0.08)	0.23 (0.09)
$P_{ET}CO_2$ (kPa)	4.0 (3.6–4.4)	3.9 (3.6–4.4)
V_E/VCO_2 slope	38 (5)	39 (8)
Surgery		
Duration of surgery (min)	145 (95–215)	126 (90–180)
Lobectomy	40 (63)	33 (57)
Bilobectomy	1 (2)	1 (2)
Atypical resection	23 (36)	25 (43)
Pneumonectomy	1 (2)	0
Open thoracotomy	29 (45)	19 (33)

Sample size

Sample size was estimated using an expected postoperative complication incidence of 75% for usual care[11] and 50% for the prehabilitation group. With $P<0.05$ and power of 0.80, 55 patients were required to be randomized to each group. Assuming a 15% dropout rate, we planned to enrol and randomly assign 130 patients.

Results

Study participants

Four hundred and seventy-four patients were screened with CPET, resulting in 132 patient being randomised (Fig. 1). Data

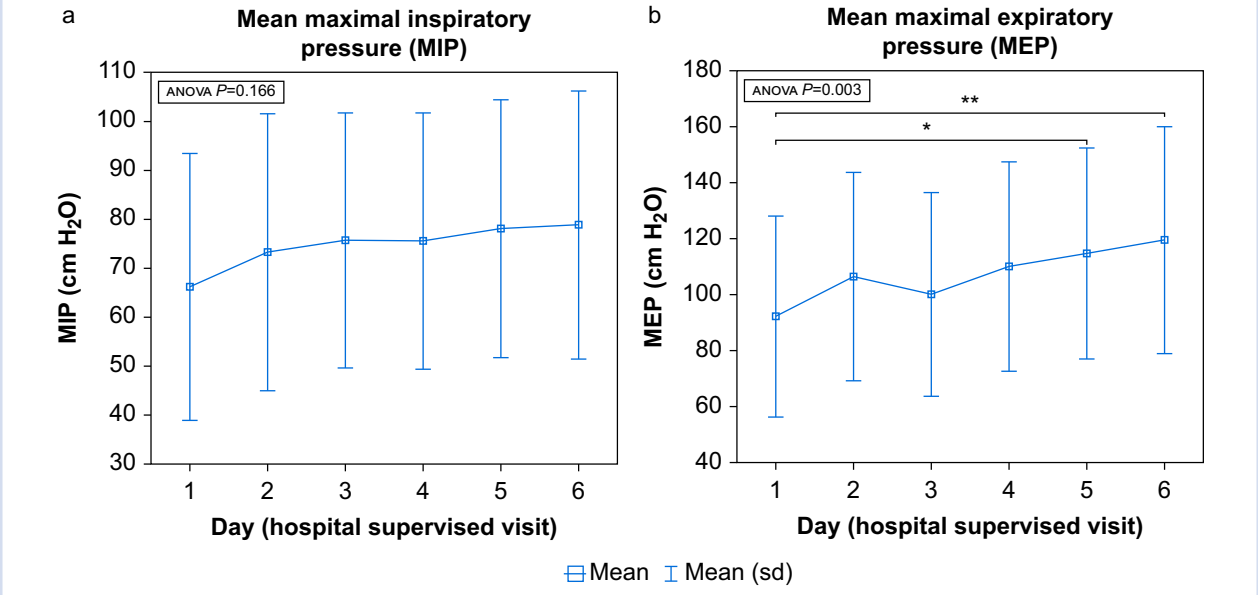

Fig 2. Effect of prehabilitation on mean maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). (a) There was no change in MIP over the six hospital-based supervised visits. (b) MEP increased with prehabilitation over the six hospital-based supervised visits. *P=0.018. **P=0.004.

from the nonrandomised patients have been reported elsewhere.[28,29] In the prehabilitation group, eight patients were excluded after randomisation, compared with two patients from the usual care group who withdrew their consent to participate (Fig. 1).

Effect of prehabilitation programme

In the prehabilitation group, the hospital-based supervised training visits were completed by all patients, with 100% self-reported compliance for home self-training (Table 1). During prehabilitation, mean maximal respiratory pressure increased over the six supervised visits (Fig. 2). After 2 weeks of prehabilitation, VO_2, VCO_2, P_{ETCO_2}, and DL_{CO} increased, with a reduction in the V_E/VCO_2 slope (Table 2; Supplementary Table S1). The prehabilitation intervention also reduced the number of active smokers (Table 2). Self-reported quality of life (EQ-5D-3L) improved with prehabilitation, whereas that of patients randomised to usual care decreased with surgery (Fig. 3). None of the patients required nutritional support.

Primary outcome

Prehabilitation reduced the composite outcome of PPCs (OR 2.29 [95% CI 1.10–4.77]), with fewer air leaks (OR 2.92 [95% CI 1.28–6.67]; Table 3).

Secondary outcomes

The duration of chest drain use and hospital length of stay were reduced in the prehabilitation group, with no difference in cardiovascular complications, compared with patients randomised to usual care (Table 3).

Table 2 Effect of multimodal prehabilitation. Data are presented as: 1) mean ± SD - FEV_1, FVC, Pa_{O2}, Pa_{CO2}, pH, fb, V_D/V_T, V_E/VCO_2 slope 2) median (interquartile range (IQR)) - Fagerstom, DL_{CO}, VO_2, VCO_2, RER, V_E, V_T, P_{ETCO_2}. DL_{CO}, diffusing capacity of the lungs for carbon monoxide; f_b, breathing frequency; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Pa_{CO2}, arterial partial pressure of carbon dioxide; Pa_{O2}, arterial partial pressure of oxygen; P_{ETCO_2}, partial pressure of end-tidal carbon dioxide; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; V_D, dead space volume; V_E, minute ventilation; V_E/VCO_2, ventilatory efficiency; VO_2, oxygen consumption; V_T, tidal volume.

Parameter	Baseline	Post prehabilitation	P
Fagerström score	0.0 (0.0–2.0)	0.0 (0.0–0.0)	0.051
Pulmonary function tests			
FEV_1 (%)	82 (18)	83 (18)	0.758
FVC (%)	93 (18)	96 (16)	0.080
DL_{CO} (%)	74 (61–89)	81 (55–99)	0.004
Arterial blood gases at peak exercise			
Pa_{O2} (kPa)	9.6 (1.7)	9.5 (1.6)	0.736
Pa_{CO2} (kPa)	4.7 (0.5)	4.9 (0.5)	0.016
pH	7.37 (0.04)	7.36 (0.03)	0.352
CPET peak exercise			
VO_2 (ml kg^{-1} min^{-1})	15.2 (13.2–18.4)	15.8 (13.2–17.8)	0.044
VCO_2 (L min^{-1})	1.3 (1.2–1.7)	1.4 (1.2–1.7)	0.015
RER	1.13 (1.05–1.24)	1.13 (1.04–1.32)	0.114
V_E (L min^{-1})	56 (47–68)	59 (48–67)	0.856
V_T (L)	1.49 (1.24–1.89)	1.51 (1.23–1.94)	0.365
f_b (bpm)	38 (7)	38 (6)	0.684
V_D/V_T	0.23 (0.09)	0.24 (0.09)	0.307
P_{ETCO_2} (kPa)	3.9 (3.6–4.4)	4.1 (3.6–4.7)	0.002
V_E/VCO_2 slope	39 (8)	36 (9)	0.010

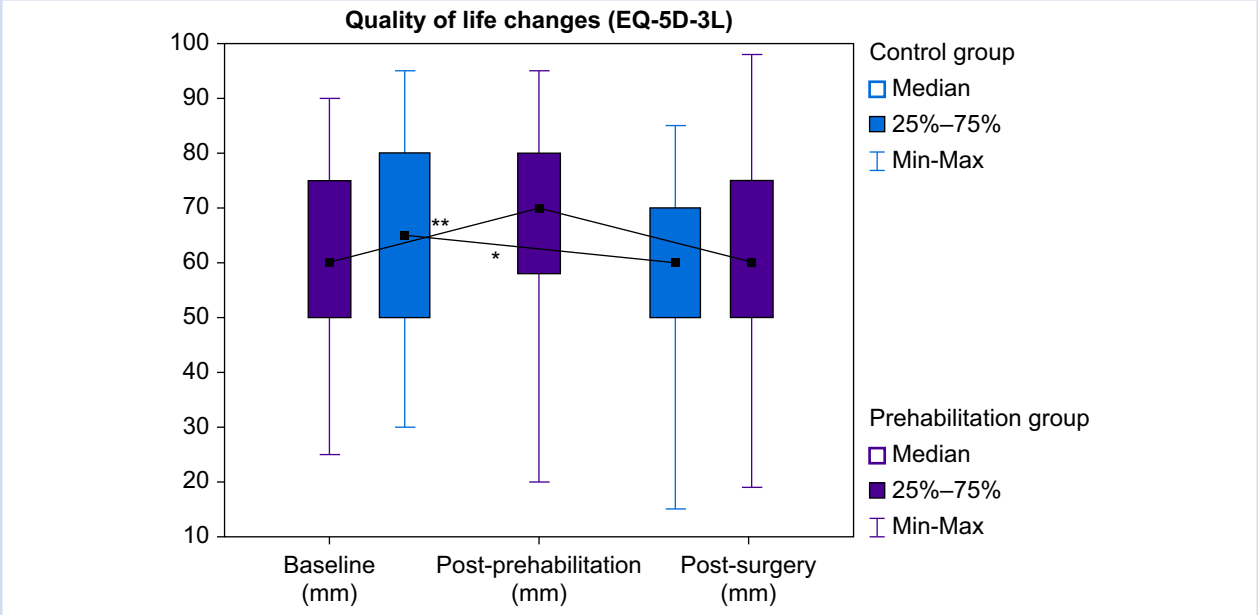

Fig 3. Quality of life changes (by EuroQol EQ-5D-3L questionnaire). In the prehabilitation group, quality of life improved from baseline (ANOVA P=0.013), characterised by a sustained improvement after prehabilitation was completed; **P=0.029. In the usual care group, quality of life declined with surgery; *P=0.004.

Table 3 Primary and secondary outcomes. Data are presented as: 1) n (%) - pulmonary complications (all of the variables), cardiovascular complications (all of the variables), ICU readmission, 30 days mortaity 2) median (interquartile range (IQR)) - hospital LOS, ICU LOS, chest drainage duration. ARDS, adult respiratory distress syndrome; LOS, length of stay; PPC, postoperative pulmonary complications.

Parameter	Usual care (*n*=64)	Prehabilitation (*n*=58)	*P*
Primary outcome: postoperative pulmonary complications			
PPC-composite	35 (55)	20 (34)	0.029
Pneumonia	17 (27)	8 (14)	0.115
Atelectasis	3 (5)	3 (5)	1.000
Respiratory failure	3 (5)	2 (3)	1.000
ARDS	0	1 (2)	0.475
Prolonged air leak	26 (41)	11 (19)	0.010
Secondary outcomes			
ICU readmission	1 (2)	3 (5)	0.345
30-days mortality	1 (2)	0	1.000
Hospital LOS (days)	9 (7–11)	7 (6–9)	0.038
ICU LOS (days)	4 (2–6)	3 (2–5)	0.271
Chest drainage duration (days)	6 (5–8)	5 (4–7)	0.039
Postoperative cardiovascular complications			
Cardiovascular complications–composite	16 (25)	12 (21)	0.668
Pulmonary oedema	0	2 (3)	0.224
Pulmonary embolism	0	0	1.000
Arrhythmia	11 (17)	8 (14)	0.628
Hypotension	9 (14)	6 (10)	0.590
Heart failure	1 (2)	2 (3)	0.604
Acute myocardial infarction	0	0	1.000
Cardiopulmonary resuscitation	1 (2)	1 (2)	1.000

Exploratory prespecified analyses

In the prehabilitation group, univariate analysis showed delta V_E/VCO_2 slope was associated with the development of PPC (OR 1.11 [95% CI 1.00–1.22]; P=0.046). No changes were observed in DL_{CO} (OR 0.98 [95% CI 0.94–1.02]; P=0.284) and peak VO_2 (OR 0.90 [95% CI 0.72–1.14]; P=0.387). Delta V_E/VCO_2 slope remained associated with the development of PPC (OR 1.11 [95% CI 1.00–1.22]; P=0.046) even after the model was adjusted for age, gender, BMI, and surgical risk (derived from the S-MPM).

Discussion

The major finding of this RCT was that 2 weeks of prehabilitation incorporating high-intensity respiratory muscle training decreased the incidence of PPCs in patients undergoing lung resection. In addition, hospital length of stay and chest drainage duration were shorter, the number of smokers decreased, and quality of life improved with prehabilitation. High-intensity respiratory muscle training also decreased the V_E/VCO_2 slope, and increased peak VO_2 and DL_{CO}. Only the change of V_E/VCO_2 slope was associated with the lower incidence of PPC in the prehabilitation group.

For the entire cohort, PPC developed in 55 (45%) patients, which is higher than previously reported[3] and may be explained by limiting inclusion to high-risk patients. Patients at high risk for PPC development were identified by V_E/VCO_2 slope $\geq$33, based on our previous study.[13] Risk stratification and selection of high-risk patients have enabled demonstration of improvements in both exercise capacity and outcomes,[1] in contrast to the RCT of Licker and colleagues,[9] where in a cohort of unselected patients early postoperative complications were not reduced by short-term high-intensity training.

The frequency of PPC was lower and associated with a decrease of V_E/VCO_2 slope in the prehabilitation group. Prolonged air leak and pneumonia were the major PPCs. Prolonged air leak is a common complication of lung resection surgery and is linked to heightened morbidity.[25] Fewer days needing a chest tube and a lower incidence of prolonged chest tubes have been previously shown in lung resection patients who underwent preoperative inspiratory muscle training.[6] Moreover, lung resection surgery patients with elevated V_E/VCO_2 slope have been shown to be prone to development of prolonged air leak,[30] probably a result of increased transalveolar pressure by dynamic hyperinflation owing to increased ventilatory drive and chronic obstructive pulmonary disease (COPD).[31] A second potential contributor, though not achieving significant difference, was pneumonia. Recently, V_D/V_T was shown to be the major contributor to increased V_E/VCO_2 in lung resection patients who subsequently developed PPC.[29] One reason for increased V_D/V_T is a rapid shallow breathing pattern[32] which may promote atelectasis, pneumonia, or both.

There was no difference in the incidence of postoperative cardiovascular complications. Although several studies showed V_E/VCO_2 slope is associated with PPC,[10,13,15] only one retrospective study showed an association between V_E/VCO_2 slope and postoperative cardiovascular complications in lung resection candidates.[12] V_E/VCO_2 is defined by the modified alveolar gas equation as $V_E/VCO_2 = 863/(Pa_{CO2} \times [1-V_D/V_T])$,[32] suggesting it is increased by low Pa_{CO2} (hyperventilation) or high V_D/V_T ratio (ventilation/perfusion mismatch or rapid and shallow breathing pattern). The physiological relationship of V_E/VCO_2 to ventilatory parameters may account for the lower incidence of PPC and the lack of improvement in cardiovascular complications in the prehabilitation group.

Peak VO_2, a marker of exercise capacity, has been fundamental to preoperative risk evaluation[19,33] and a frequent target of previous prehabilitation programmes.[1,8,9] In our cohort, peak VO_2 significantly increased with prehabilitation. However, this increase was not associated with reduced PPC. This observation is in agreement with the study of Licker and colleagues[9] showing exercise training improved aerobic performance (peak VO_2) but not early complications after lung resection. Indeed, several studies have shown peak VO_2 to be a poor predictor of PPC,[14] especially compared with V_E/VCO_2 slope.[10–13] For lung resection surgery, V_E/VCO_2 slope has been found to be an excellent predictor of PPC,[10,13,15] establishing the rationale for selection of this parameter as a target of our prehabilitation programme, using the high-intensity respiratory muscle training.[17] In our cohort, prehabilitation decreased V_E/VCO_2 slope and this was associated with reduced PPC. In the trial by Licker and colleagues,[9] V_E/VCO_2 slope did not improve with prehabilitation in an unselected group of patients and may have contributed to the inability to reduce PPC in their study.

For lung resection surgery, PFTs predict the risk of PPC.[34] In our study, DL_{CO} improved with prehabilitation. However, the improvement of DL_{CO} was not associated with less PPC. Similarly, in a recent study Dankert and colleagues[35] showed that PFT did not provide additional prognostic value in patients with COPD before lung resection surgery. Moreover, DL_{CO} has been shown to predict PPC only after open thoracotomy, but not after VATS.[36] In our cohort, more than half of patients underwent VATS and this may explain the lack of association of DL_{CO} with PPC. The number of smokers decreased as did nicotine dependence in the prehabilitation group. This is in agreement with previous studies showing the preoperative period to be an opportunity to initiate smoking cessation.[37] Quality of life also improved in the prehabilitation group which is in agreement with studies showing that physical exercise and breathing relaxation techniques improve quality of life.[38,39]

Our study has several limitations. First, our study was not powered to detect a mortality difference between groups. Second, there was missing data; PFTs were not done in five patients post prehabilitation and arterial blood gas analysis was not available for 21 patients because of patients' refusal or technical difficulties. Two patients refused to fill in the EQ-5D-3L and Fagerström questionnaire before prehabilitation and one after prehabilitation. Data imputation was not performed. Third, the generalisability for our findings is limited as only high-risk patients were selected. Fourth, although data gathering researchers and caretaking physicians were blinded to the randomisation results, necessary postponements of surgery in some patients may have meant that blinding was not effective for caretaking physicians. Fifth, the fragility index of this trial is 2. Sixth, there were substantial differences in pleural effusion management by thoracic surgeons, which may have biased chest drainage duration. Conversely, prolonged air leak is an objective and well-defined PPC.

In summary, in high-risk patients, 2 weeks of prehabilitation based on high-intensity respiratory muscle

training reduced postoperative pulmonary complications and hospital length of stay, with an associated improvement in quality of life.

Authors' contributions

Study design: KB and IC
Registered the CMRD project at ClinicalTrials.gov.: IC
Secured funding for the research project: IC Jr, KB, MilS
Data collection within the centres: KB, PH, MP, SG, AP, FD, BI, ZCh, LM, MM, MichS, LJO, IC
Data collection, analysis, and interpretation: all authors
Designed the analyses: KB, IC, MichS
Statistical analysis: MichS
Writing of the manuscript: all authors
Drafted the manuscript: KB, MichS, IC
Critically revised the manuscript for intellectual content and approved the final submitted version: all authors

Acknowledgements

The authors thank all patients participating in this study for sharing their data with the scientific community.

Declaration of interest

The authors declare that they have no conflict of interest.

Funding

Ministry of Health of the Czech Republic research grant (NU21-06-00086). Funding sources had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2025.03.018.

References

1. Sanchez-Lorente D, Navarro-Ripoll R, Guzman R, et al. Prehabilitation in thoracic surgery. *J Thorac Dis* 2018; **1**: S2593–600
2. Baser S, Shannon VR, Eapen GA, et al. Pulmonary dysfunction as a major cause of inoperability among patients with non-small-cell lung cancer. *Clin Lung Cancer* 2006; **7**: 344–9
3. Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? *Thorax* 2010; **65**: 815–8
4. Dean HF, Carter F, Francis NK. Modern perioperative medicine – past, present, and future. *Innov Surg Sci De Gruyter* 2019; **4**: 123–31
5. Sekine Y, Chiyo M, Iwata T, et al. Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Jpn J Thorac Cardiovasc Surg* 2005; **53**: 237–43
6. Benzo R, Wigle D, Novotny P, et al. Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. *Lung Cancer Amst Neth* 2011; **74**: 441–5
7. Gao K, Yu P-M, Su J-H, et al. Cardiopulmonary exercise testing screening and pre-operative pulmonary rehabilitation reduce postoperative complications and improve fast-track recovery after lung cancer surgery: a study for 342 cases. *Thorac Cancer* 2015; **6**: 443–9
8. Boujibar F, Bonnevie T, Debeaumont D, et al. Impact of prehabilitation on morbidity and mortality after pulmonary lobectomy by minimally invasive surgery: a cohort study. *J Thorac Dis* 2018; **10**: 2240–8
9. Licker M, Karenovics W, Diaper J, et al. Short-term preoperative high-intensity interval training in patients awaiting lung cancer surgery: a randomized controlled trial. *J Thorac Oncol* 2017; **12**: 323–33
10. Brunelli A, Belardinelli R, Pompili C, et al. Minute ventilation-to-carbon dioxide output (VE/VCO2) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *Ann Thorac Surg* 2012; **93**: 1802–6
11. Brat K, Tothova Z, Merta Z, et al. Resting end-tidal carbon dioxide predicts respiratory complications in patients undergoing thoracic surgical procedures. *Ann Thorac Surg* 2016; **102**: 1725–30
12. Mazur A, Brat K, Homolka P, et al. Ventilatory efficiency is superior to peak oxygen uptake for prediction of lung resection cardiovascular complications. *PLoS One* 2022; **17**, e0272984
13. Brat K, Homolka P, Merta Z, et al. Prediction of postoperative complications: ventilatory efficiency and rest end-tidal carbon dioxide. *Ann Thorac Surg* 2023; **115**: 1305–11
14. Begum SSS, Papagiannopoulos K, Falcoz PE, Decaluwe H, Salati M, Brunelli A. Outcome after video-assisted thoracoscopic surgery and open pulmonary lobectomy in patients with low VO 2 max : a case-matched analysis from the ESTS database. *Eur J Cardiothorac Surg* 2016; **49**: 1054–8
15. Rushwan A, Stefanou D, Tariq J, et al. Increased minute ventilation to carbon dioxide slope during cardiopulmonary exercise test is associated with poor postoperative outcome following lung cancer resection. *Eur J Cardiothorac Surg* 2024; **65**: ezad337
16. Gravier F-E, Bonnevie T, Boujibar F, et al. Effect of prehabilitation on ventilatory efficiency in non-small cell lung cancer patients: a cohort study. *J Thorac Cardiovasc Surg* 2019; **157**. 2504–25012.e1
17. Kasahara Y, Izawa KP, Watanabe S, Osada N, Omiya K. The relation of respiratory muscle strength to disease severity and abnormal ventilation during exercise in chronic heart failure patients. *Res Cardiovasc Med* 2015; **4**, e28944
18. Hulzebos EHJ, Helders PJM, Favié NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NLU. 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
19. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 2009; **34**: 17–41
20. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J* 2005; **26**: 153–61
21. EuroQol. EQ-5D-3L. Available from: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-3l/ (accessed 01 November 2024).
22. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of

the Fagerström Tolerance Questionnaire. *Br J Addict* 1991; **86**: 1119–27
23. Stéphan F, Boucheseiche S, Hollande J, et al. Pulmonary complications following lung resection: a comprehensive analysis of incidence and possible risk factors. *Chest* 2000; **118**: 1263–70
24. Licker MJ, Widikker I, Robert J, et al. Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg* 2006; **81**: 1830–7
25. Brunelli A, Cassivi SD, Halgren L. Risk factors for prolonged air leak after pulmonary resection. *Thorac Surg Clin* 2010; **20**: 359–64
26. Bennett-Guerrero E, Welsby I, Dunn TJ, et al. The use of a postoperative morbidity survey to evaluate patients with prolonged hospitalization after routine, moderate-risk, elective surgery. *Anesth Analg* 1999; **89**: 514–9
27. Kazimierczak S, Rybicka A, Strauss J, Schram M, Kazimierczak A, Grochans E. External validation of the Surgical Mortality Probability Model (S-MPM) in patients undergoing non-cardiac surgery. *Ther Clin Risk Manag* 2019; **15**: 1173–82
28. Svoboda M, Cundrle I, Plutinsky M, et al. New models for prediction of post-operative pulmonary complications in lung resection candidates. *ERJ Open Res* 2024; **10**: 978–2023
29. Bartos S, Svoboda M, Brat K, et al. Causes of ventilatory inefficiency in lung resection candidates. *ERJ Open Res* 2025; **11**: 792–2024
30. Brat K, Chobola M, Homolka P, et al. Poor ventilatory efficiency during exercise may predict prolonged air leak after pulmonary lobectomy. *Interact Cardiovasc Thorac Surg* 2020; **30**: 269–72
31. Gatta D, Fredi M, Aliprandi G, Pini L, Tantucci C. Inspiratory drive is related to dynamic pulmonary hyperinflation in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2013; **8**: 169–73
32. Woods PR, Olson TP, Frantz RP, Johnson BD. Causes of breathing inefficiency during exercise in heart failure. *J Card Fail* 2010; **16**: 835–42
33. 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**. e166S-90S
34. Almquist D, Khanal N, Smith L, Ganti AK. Preoperative pulmonary function tests (PFTs) and outcomes from resected early stage non-small cell lung cancer (NSCLC). *Anticancer Res* 2018; **38**: 2903–7
35. Dankert A, Neumann-Schirmbeck B, Dohrmann T, et al. Preoperative spirometry in patients with known or suspected chronic obstructive pulmonary disease undergoing major surgery: the prospective observational PREDICT study. *Anesth Analg* 2023; **137**: 806
36. Berry MF, Villamizar-Ortiz NR, Tong BC, et al. Pulmonary function tests do not predict pulmonary complications after thoracoscopic lobectomy. *Ann Thorac Surg* 2010; **89**: 1044–52
37. Pierre S, Rivera C, Le Maître B, et al. Guidelines on smoking management during the perioperative period. *Anaesth Crit Care Pain Med* 2017; **36**: 195–200
38. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012; **2012**: CD008465
39. Liu Y, Jiang T, Shi T, et al. The effectiveness of diaphragmatic breathing relaxation training for improving sleep quality among nursing staff during the COVID-19 outbreak: a before and after study. *Sleep Med* 2020; **78**: 8

Handling editor: Gareth Ackland