The risk of post-operative pulmonary complications in lung resection candidates with normal forced expiratory volume in 1 s and diffusing capacity of the lung for carbon monoxide: a prospective multicentre study

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Shareable abstract (@ERSpublications)
In addition to FEV_1 and D_{LCO}, resting P_{ETCO_2} and V'_E/V'_{CO_2} slope deliver additional information on risk of post-operative pulmonary complication development in lung resection candidates
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Abstract

Introduction According to the guidelines for preoperative assessment of lung resection candidates, patients with normal forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) are at low risk for post-operative pulmonary complications (PPC). However, PPC affect hospital length of stay and related healthcare costs. We aimed to assess risk of PPC for lung resection candidates with normal FEV_1 and D_{LCO} (>80% predicted) and identify factors associated with PPC.

Methods 398 patients were prospectively studied at two centres between 2017 and 2021. PPC were recorded from the first 30 post-operative days. Subgroups of patients with and without PPC were compared and factors with significant difference were analysed by uni- and multivariate logistic regression.

Results 188 subjects had normal FEV_1 and D_{LCO}. Of these, 17 patients (9%) developed PPC. Patients with PPC had significantly lower pressure of end-tidal carbon dioxide (P_{ETCO_2}) at rest (27.7 *versus* 29.9; p=0.033) and higher ventilatory efficiency (V'_E/V'_{CO_2}) slope (31.1 *versus* 28; p=0.016) compared to those without PPC. Multivariate models showed association between resting P_{ETCO_2} (OR 0.872; p=0.035) and V'_E/V'_{CO_2} slope (OR 1.116; p=0.03) and PPC. In both models, thoracotomy was strongly associated with PPC (OR 6.419; p=0.005 and OR 5.884; p=0.007, respectively). Peak oxygen consumption failed to predict PPC (p=0.917).

Conclusions Resting P_{ETCO_2} adds incremental information for risk prediction of PPC in patients with normal FEV_1 and D_{LCO}. We propose resting P_{ETCO_2} be an additional parameter to FEV_1 and D_{LCO} for preoperative risk stratification.

Introduction

According to the most recent European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS) guidelines for preoperative assessment of lung resection candidates, spirometry and assessment of diffusing capacity of the lung for carbon monoxide (D_{LCO}) should be part of routine diagnostic evaluation

prior to thoracic surgery [1]. In cases where forced expiratory volume in 1 s (FEV_1) or D_{LCO} is lower than 80% of predicted, cardiopulmonary exercise testing (CPET) is also recommended [1].

Despite widespread use of less invasive surgical techniques (video-assisted and non-intubation thoracic surgery) over the last decade, peri-operative morbidity and mortality rates remain high compared to other elective surgical procedures. The reported 30-day post-operative mortality rates after pulmonary resection range from 2.1% to 3% [2–4] and as high as 6.6% [5] to 7.5% [6]. In contrast, reported 30-day mortality rates after cholecystectomy are 0.15% [7] and 0.08% for elective appendectomy [8]. Post-operative pulmonary complications (PPC) not only promote intensive care unit (ICU) readmission and prolonged hospital stay with adverse economic impact, but they also contribute to peri-operative mortality following lung resection [2].

Guided by current ERS/ESTS criteria for preoperative risk assessment, patients with FEV_1 and D_{LCO} >80% predicted are considered safely resectable up to the extent of pneumonectomy without further functional considerations [1]. However, it is unclear what proportion of patients with normal (>80% predicted) FEV_1 and D_{LCO} experience PPC after lung resection and which factors may be predictive of PPC in this patient subgroup.

Based on previous research demonstrating ventilatory efficiency (V'_E/V'_{CO_2}) slope and resting pressure of end-tidal carbon dioxide (P_{ETCO_2}) are independent predictors of PPC [5, 9–11], we hypothesised that these parameters may predict PPC in the subgroup of patients with normal preoperative lung function (FEV_1 and D_{LCO} ⩾80% predicted). Therefore, the aims of this study were to: 1) assess frequency of PPC in patients with normal FEV_1 and D_{LCO} scheduled for elective lung resection; and 2) identify factors associated with increased risk of PPC in this subgroup.

Methods

Study population

This was a prospective multicentre observational study including adult patients scheduled for lung resection surgery (mainly due to suspected or confirmed malignancy) at two tertiary-care (university type) centres in the Czech Republic (St. Anne's University Hospital in Brno and University Hospital Brno). Patient recruitment took place between May 2017 and September 2021. All patients scheduled for thoracic surgery were systematically screened for eligibility to participate in this observational study.

Inclusion criteria included written informed consent for participation, ability to undergo CPET, adult age (⩾18 years) and lung resection surgery. Exclusion criteria included inability or patient refusal to undergo CPET, contraindication for lung resection due to predicted post-operative (ppo)-peak oxygen consumption (peak V'_{O_2}) <10 $mL \cdot kg^{-1} \cdot min^{-1}$ or <35% predicted, or ppo-FEV_1 or D_{LCO} <30% predicted (in accordance with the latest ERS/ESTS guidelines [1]). The study was conducted in accordance with the declaration of Helsinki and approvals were obtained from both institutional review boards including the Ethics Committee of the University Hospital Brno (reference code 150617/EK) and Ethics Committee of St. Anne's University Hospital in Brno (reference codes 19JS/2017 and 2G/2018). The study registration reference code (ClinicalTrials.gov) is NCT03498352.

Pulmonary function tests and cardiopulmonary exercise testing

The same CPET protocol was used as in our previous published studies [11, 12]. Briefly, each patient underwent preoperative spirometry, D_{LCO} assessment and CPET. Spirometry (ZAN100 device; nSpire Health, Inc., Longmont, CO, USA) and D_{LCO} assessments (PowerCube Diffusion+ device; Ganshorn Medizin Electronic GmbH, Niederlauer, Germany) were performed in agreement with current ERS standards and technical requirements [13].

Symptom-limited CPET to volitional fatigue to a rating of perceived exertion of 18 to 20 on the Borg scale was used in each patient on an electronically braked bicycle ergometer (Ergometrics 800®; Ergoline, Bitz, Germany) with an incorporated 12-channel electrocardiography unit (AT-104®; Schiller AG, Baar, Switzerland). The expired gases and volumes were analysed using the PowerCube-Ergo® system (Ganshorn Medizin Electronic GmbH, Niederlauer, Germany). The CPET protocol included a rest phase, warm-up phase and ramp protocol with linearly increasing resistance (15 $W \cdot min^{-1}$) with 3-min cool-down.

The following parameters were recorded: FEV_1, forced vital capacity (FVC), FEV_1/FVC (spirometry), D_{LCO}, V'_{O_2}, carbon dioxide output (V'_{CO_2}), tidal volume (V_T), breathing frequency (fb), minute ventilation (V'_E), P_{ETCO_2}, dead space ventilation to tidal volume ratio (V_D/V_T), respiratory exchange ratio (RER), V'_E/V'_{CO_2} ratio and V'_E/V'_{CO_2} slope (calculated up to peak exercise).

Post-operative pulmonary complications

PPC were recorded prospectively from the first 30 post-operative days or from the hospital stay. The PPC were defined similarly to previous studies [9, 11, 12, 14] and included: respiratory failure (requiring noninvasive ventilation or intubation plus invasive mechanical ventilation); acute respiratory distress syndrome (bilateral chest radiograph infiltrates not due to fluid overload or cardiac failure plus partial pressure of oxygen in arterial blood/inspiratory oxygen fraction (P_{aO_2}/F_{IO_2}) <300); tracheostomy; pneumonia (chest radiograph infiltrates plus at least two of the following signs: purulent sputum or fever or leukocytosis/leukopenia) and atelectasis (chest radiograph signs plus urgent bronchoscopy with removal of mucus plug). 30-day mortality and hospital and ICU length of stay (LOS) were also monitored.

Statistical analyses

Categorical parameters were described by absolute and relative frequencies. Continuous parameters were described by mean±SD and median supplemented by 5% quantile and 95% quantile. Statistically significant differences between two groups (with and without complications) were tested by Pearson chi-square test (Fisher exact test) for categorical and t-test (Mann–Whitney test) for continuous parameters.

Univariate logistic regression was used to identify risk factors of PPC in the subgroup of patients with FEV_1 and D_{LCO} ⩾80%. Receiver operating characteristic (ROC) analysis was used to determine which parameters are useful to divide the patients into two groups according to presence of PPC. Cut-offs were chosen as the highest sum of sensitivity and specificity.

To prevent collinearity of P_{ETCO_2} and V'_E/V'_{CO_2}, we created two models for multivariate regression analysis separately for each parameter, and both models also contained thoracotomy as the strongest factor from the univariate analysis. Multivariate models adjusted by age, sex, thoracotomy, FEV_1/FVC and D_{LCO} were also calculated (see supplementary material). A forward stepwise method was used to obtain the final models. ROC analysis for comparison of both models was provided. Comparison of area under the curve (AUC) was performed by the DeLong test; p-values <0.05 were considered statistically significant. SPSS Statistics 25.0 (IBM Corp, Chicago, IL, USA) was used for analysis.

Results

The study cohort comprised 423 patients. Of these, 398 had complete data on lung function, D_{LCO} and CPET and were further analysed (figure 1).

Of the 398 analysed subjects, 188 had values of FEV_1 and D_{LCO} ⩾80% predicted. Subgroups of patients with normal FEV_1 and D_{LCO} (⩾80% predicted) or FEV_1 and/or D_{LCO} <80% predicted had comparable age, body mass index and proportion of men. Differences between the subgroups were observed for CPET variables as the subgroup with normal FEV_1 and D_{LCO} had significantly lower V'_E/V'_{CO_2} slope, higher

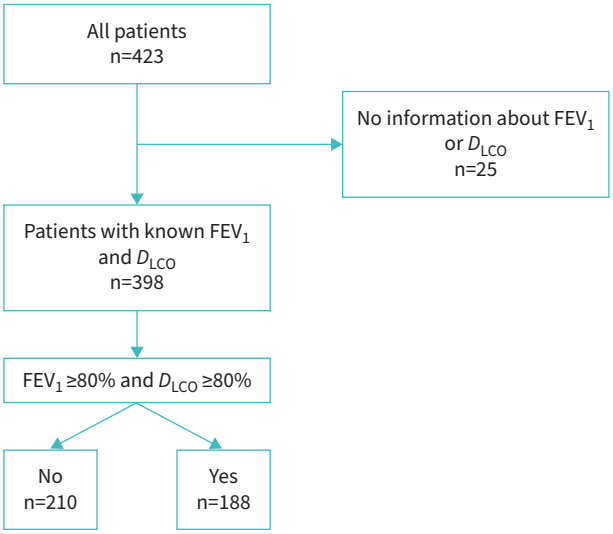

FIGURE 1 Flowchart of the study. D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s.

TABLE 1 Comparison of patient groups according to FEV_1 and D_{LCO}

	FEV_1 ⩾80% and D_{LCO} ⩾80%		p-value
	No	Yes	
Patients n	210	188	
Male sex n (%)	117 (55.7)	107 (56.9)	0.81
Age years	63.8±11.6	61.1±13.8	0.051
BMI kg·m^{-2}	28±5.8	27.8±5.2	0.795
Thoracotomy n (%)	125 (59.5)	88 (46.8)	**0.011**
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	18 (10.9–27.5)	21.3 (13.2–35.7)	**<0.001**
V'_E/V'_{CO_2} slope	32.1 (23.9–44.1)	27.7 (20.1–37.5)	**<0.001**
Resting P_{ETCO_2} mmHg	28.1 (20.4–36)	30 (21.3–36.1)	**<0.001**
Post-operative pulmonary complications n (%)	40 (19)	17 (9)	**0.004**

Normally distributed data are presented as mean±SD; non-normally distributed data as median (5th–95th percentile). Significant differences are in bold. D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; BMI: body mass index; peak V'_{O_2}: peak oxygen consumption; V'_E/V'_{CO_2} slope: ventilatory efficiency for carbon dioxide slope; resting P_{ETCO_2}: pressure of end-tidal carbon dioxide at rest.

peak V'_{O_2}, higher P_{ETCO_2} and lower proportion of thoracotomy procedures. The subgroup with normal FEV_1 and D_{LCO} had about half the rate of PPC compared to the subgroup with decreased FEV_1 and/or D_{LCO} (9% *versus* 19%; p=0.004). A summary of patient characteristics for both subgroups is presented in table 1.

Of the 188 subjects with normal FEV_1 and D_{LCO}, 17 patients (9%) developed PPC. Patients in the subgroup with PPC had thoracotomy more frequently (82.4% *versus* 43.3%; p=0.004), had longer hospital and ICU LOS (12.35 *versus* 6.67 days and 7 *versus* 3.08 days; p<0.001 for both) and higher preoperative V'_E/V'_{CO_2} slope (31.1 *versus* 28; p=0.016) and lower resting P_{ETCO_2} (27.7 *versus* 29.9; p=0.033) compared to patients without PPC. The values of peak V'_{O_2} were similar between the two subgroups (p=0.913) (table 2).

Univariate logistic regression analysis demonstrated thoracotomy, resting P_{ETCO_2} and V'_E/V'_{CO_2} slope were associated with PPC (supplementary table S1). For model 1, multivariate analysis showed thoracotomy and resting P_{ETCO_2} (OR 6.419 and 0.872, respectively) were significant risk factors, while for model 2 thoracotomy and V'_E/V'_{CO_2} slope (OR 5.884 and 1.116, respectively) were independently associated with PPC (table 3). AUCs of these models were comparable (0.767 *versus* 0.781; p=0.617) (figure 2). Adjustment by age, sex, thoracotomy, FEV_1/FVC and D_{LCO} did not significantly change the result of the multivariate analysis (supplementary table S2). Ideal cut-off values for PPC prediction were ⩽30.5 mmHg for resting P_{ETCO_2} and ⩾28.1 for V'_E/V'_{CO_2} slope (table 2).

Discussion

The novel finding of our study was that 9% of patients with normal FEV_1 and D_{LCO} according to current preoperative assessment guidelines [1, 15] developed PPC. These patients exhibited preoperative signs of impaired ventilatory control (lower resting P_{ETCO_2} and increased V'_E/V'_{CO_2} slope) that may be used for risk stratification. Importantly, peak V'_{O_2} failed to predict PPC in this specific subgroup.

The key functional measurements to assess preoperative fitness for radical thoracic surgery have been spirometry and D_{LCO} examination. Predictive values of FEV_1 and D_{LCO} have been studied extensively and both are well established in preoperative functional assessment algorithms [1, 15]. The discriminative power of these parameters is stronger in patients with low values of FEV_1 and/or D_{LCO} but the test performance decreases with increasing values [1]. In our study, the rates of PPC were doubled in patients with decreased FEV_1 and D_{LCO} compared to those with normal values of both parameters. This finding confirms that the diagnostic utility of both parameters for basic risk assessment is high. On the other hand, even in the subgroup with normal FEV_1 and D_{LCO}, there were significant numbers of patients who developed PPC. Importantly, there were no differences in FEV_1 and D_{LCO} on comparison of patients with and without PPC, which suggests the need for additional predictors if improvements in patient management and outcomes are to be achieved.

A proposed strategy to improve outcomes in the post-operative period might be more precise identification of patients at risk of PPC development. The potential role of another possible strategy – prehabilitation prior to thoracic surgery – remains controversial and unresolved to this date and should be further

TABLE 2 Characteristics of subgroups with and without post-operative pulmonary complications

	Post-operative pulmonary complications		p-value
	No	Yes	
Patients n	171	17	
Age years	60.8±14.2	64±9.2	0.645
Male sex n (%)	98 (57.3)	9 (52.9)	0.8
BMI kg·m^{-2}	27.2 (20–37.2)	28.4 (21.9–41.5)	0.172
ASA n (%)			0.408
I	8 (4.7)	0 (0)	
II	89 (52.4)	7 (41.2)	
III	69 (40.6)	9 (52.9)	
IV	4 (2.4)	1 (5.9)	
Pneumonectomy n (%)	2 (1.2)	0 (0)	0.999
Bilobectomy n (%)	6 (3.5)	0 (0)	0.999
Thoracotomy n (%)	74 (43.3)	14 (82.4)	**0.004**
Hypertension n (%)	81 (47)	8 (47)	1.00
Ischaemic heart disease n (%)	13 (8)	2 (12)	0.63
COPD/asthma n (%)	17 (10)	1 (6)	0.71
Diabetes mellitus n (%)	24 (14)	2 (12)	1.00
Stroke n (%)	4 (2)	1 (6)	0.38
FEV_1 L	2.84 (1.83–4.56)	2.85 (1.44–3.9)	0.545
FEV_1 % pred	100 (82–128)	101 (81–118)	0.939
FVC L	3.52 (2.27–5.47)	3.92 (1.99–4.49)	0.831
FVC % pred	99 (81–137)	101 (90–128)	0.423
FEV_1/FVC %	83 (70–109)	81 (71–99)	0.455
D_{LCO} % pred	96 (81–125)	87 (81–129)	0.097
pre-CPET rest P_{aO_2} kPa	10.8 (8.5–12.9)	10.3 (9.3–11.7)	**0.017**
pre-CPET rest Oxy index	383.9 (286.8–461)	368 (330.7–417.9)	0.086
pre-CPET rest O_2 sat	97.1 (93.1–98.2)	96.6 (95.5–97.7)	0.308
pre-CPET rest P_{aCO_2} kPa	4.79 (3.99–5.37)	4.83 (3.61–5.23)	0.621
pre-CPET rest pH	7.45±0.03	7.45±0.03	0.991
CPET peak P_{aO_2} kPa	11.8 (9.8–13.4)	11.4 (9–13.2)	0.152
CPET peak Oxy index	422.5 (349.9–482.1)	399 (300–471.4)	0.059
CPET peak O_2 sat	96.8 (93.9–98.1)	96.6 (92.9–97.7)	0.254
CPET peak P_{aCO_2} kPa	4.71 (3.88–5.6)	4.67 (3.31–5.84)	0.856
CPET peak pH	7.36±0.04	7.37±0.04	0.672
Rest phase s	80 (30–140)	75 (10–90)	0.289
Rest V'_{O_2} mL·kg^{-1}·min^{-1}	4.2 (2.4–6.6)	3.9 (1.8–7.8)	0.297
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	21.2 (13.4–35.5)	23.4 (12.7–41.1)	0.913
Rest oxygen pulse mL/beat	3.9 (3.1–4.9)	3.3 (2.7–4.9)	0.84
Peak oxygen pulse mL/beat	11.5 (9.3–15.2)	11.8 (9.5–17.8)	0.85
Rest V'_{CO_2} L·min^{-1}	0.26 (0.12–0.41)	0.21 (0.08–0.47)	0.062
Peak V'_{CO_2} L·min^{-1}	1.77 (1.11–3.09)	1.67 (1.26–2.78)	0.36
Rest RER	0.77 (0.54–0.95)	0.63 (0.51–0.91)	**0.001**
Peak RER	1.1 (0.75–1.27)	0.93 (0.69–1.18)	**0.028**
Rest V'_E L·min^{-1}	10.2 (4.9–15.8)	7.8 (2.3–22.9)	**0.042**
Peak V'_E L·min^{-1}	56.6 (34.2–95)	58.4 (38.5–97.2)	0.865
Rest V_T L	0.58 (0.24–0.98)	0.44 (0.13–1.18)	**0.017**
Peak V_T L	1.88 (1.13–2.81)	1.58 (1.11–2.9)	0.499
Rest fb	18 (10–28)	19 (11–30)	0.325
Peak fb	31 (23–42)	34 (17–46)	0.053
Rest V_D/V_T	0.29 (0.12–0.43)	0.24 (0.08–0.4)	0.417
Peak V_D/V_T	0.19 (0.08–0.3)	0.18 (0.08–0.32)	0.989
Rest P_{ETCO_2} mmHg	30.1 (22.1–36.5)	28.8 (20.6–31.9)	**0.033**
Peak P_{ETCO_2} mmHg	35.5 (26.2–43.1)	34.7 (22.1–39.3)	0.262
V'_E/V'_{CO_2} slope	27.6 (20.1–36.8)	30.2 (23.5–40.2)	**0.016**
Rest V'_E/V'_{CO_2} ratio	38.6 (31.3–52.5)	41.8 (29–48.8)	0.403
Peak V'_E/V'_{CO_2} ratio	31.8 (25.6–39.6)	33.6 (26.8–47.8)	**0.028**
Hospital LOS days	6 (3–13)	12 (4–30)	**<0.001**
ICU LOS days	3 (1–7)	7 (3–16)	**<0.001**
Duration of chest drainage days	4 (3–8)	7 (3–27)	**0.001**

Continued

TABLE 2 Continued

Categorical parameters are described by absolute and relative frequencies. Normally distributed data are presented as mean±SD; non-normally distributed data as median (5th–95th percentile). Significant differences are in bold. BMI: body mass index; ASA: American Society of Anesthesiologists physical status class; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; CPET: cardiopulmonary exercise testing; P_{aO_2}: partial pressure of oxygen in arterial blood; Oxy index: oxygenation index; O_2 sat: peripheral oxygen saturation; P_{aCO_2}: partial pressure of carbon dioxide in arterial blood; V'_{O_2}: oxygen consumption; V'_{CO_2}: carbon dioxide production; RER: respiratory exchange ratio; V'_E: minute ventilation; V_T: tidal volume; fb: breathing frequency; V_D/V_T: dead space ventilation to tidal volume ratio; V'_E/V'_{CO_2} slope: ventilatory efficiency for carbon dioxide slope; rest P_{ETCO_2}: pressure of end-tidal carbon dioxide at rest; LOS: length of stay; ICU: intensive care unit.

investigated in the future [16]. Our data show that in patients with normal FEV_1 and D_{LCO} scheduled for thoracotomy, V'_E/V'_{CO_2} slope and resting P_{ETCO_2} are strong predictors of PPC. The diagnostic utility of V'_E/V'_{CO_2} slope in patients with decreased FEV_1 and D_{LCO} has been demonstrated over the last decade by several research groups, as they independently predict PPC [5, 9, 10], prolonged airleak [12] and 30-day mortality [14, 17]. Our research group also recently demonstrated excellent performance of P_{ETCO_2} at rest for PPC prediction [5, 11].

The main determinants of low P_{ETCO_2} are hyperventilation and increased dead space ventilation (ventilation/perfusion mismatch). In our patients, P_{aCO_2} was not significantly different between both groups, suggesting ventilation/perfusion mismatch may be the reason for low P_{ETCO_2} in the PPC group and may also explain its superiority compared to P_{aCO_2} in the PPC prediction. Indeed, V'_E/V'_{CO_2} is also related to hyperventilation (P_{aCO_2}) and dead space ventilation (V_D/V_T ratio) [18]. As there were no differences in the P_{aCO_2}, the observed difference in the V'_E/V'_{CO_2} slope must have been caused by changes in the ventilation/perfusion mismatch, *i.e.* V_D/V_T. However, we must acknowledge that no differences were observed also in the V_D/V_T ratio in our study. This may be explained by direct measurement of P_{aCO_2} *versus* underestimation of V_D/V_T [19].

In the subgroup of patients with normal FEV_1 and D_{LCO} (⩾80% predicted), the predictive properties of V'_E/V'_{CO_2} slope and resting P_{ETCO_2} were comparable (AUCs 0.767 and 0.781). This is in agreement with previous research of our work group in an unselected lung surgery patient population [11], as both parameters are determined by similar physiology [5, 11, 18, 20, 21]. Indeed, the two parameters showed a strong inverse correlation and can be used as mutual surrogates [5, 11].

Our results showed different optimal cut-off values for V'_E/V'_{CO_2} slope (28.1) and P_{ETCO_2} at rest (30.5 mmHg) compared to previous reports [5, 9–11]. For V'_E/V'_{CO_2} slope, values of 35 were reported most frequently as optimal cut-offs [5, 9–11], while for resting P_{ETCO_2}, the reported cut-offs were 30 mmHg [5] and, more recently, 28.4 mmHg [11]. The observed variability of cut-offs (more pronounced in the case of V'_E/V'_{CO_2} slope) may be explained by different composition of our study cohort, as this subgroup analysis contained only data of healthier subjects with normal lung functions (FEV_1 and D_{LCO}). We suggest that the observed cut-offs be limited to this specific subgroup of healthier patients.

Importantly, peak V'_{O_2} failed to predict PPC. This finding is in agreement with our previous study in unselected lung surgery candidates [11] and extends the series of previous reports where the predictive value of peak V'_{O_2} has been questioned [5, 9–11, 14, 17]. It is known that peak V'_{O_2} is determined by a

TABLE 3 Multivariate logistic regression: post-operative pulmonary complications

	Model 1		Model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Thoracotomy	6.419 (1.749–23.560)	**0.005**	5.884 (1.612–21.474)	**0.007**
Rest P_{ETCO_2} mmHg	0.872 (0.768–0.990)	**0.035**		
V'_E/V'_{CO_2} slope			1.116 (1.011–1.232)	**0.030**

Significant differences are in bold. CI: confidence interval; OR: odds ratio; rest P_{ETCO_2}: pressure of end-tidal carbon dioxide at rest; V'_E/V'_{CO_2} slope: ventilatory efficiency for carbon dioxide slope.

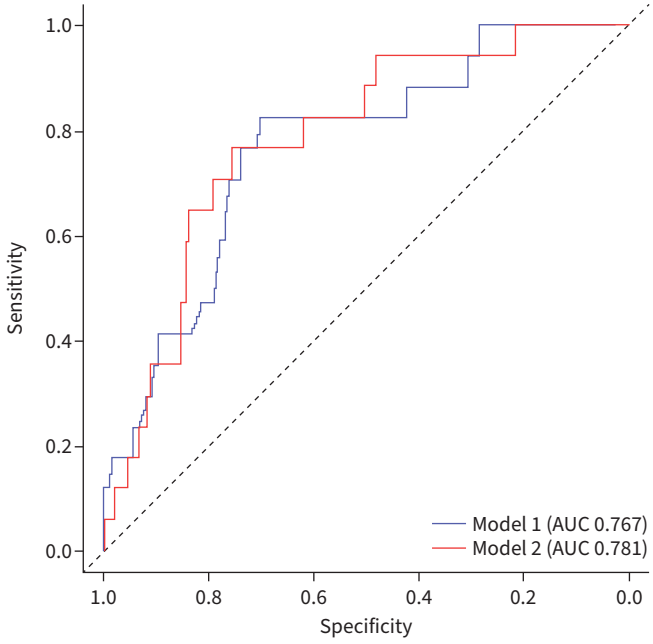

FIGURE 2 Multivariate regression models for post-operative pulmonary complication prediction. AUC: area under the curve.

wider range of factors (including cardiac output, vascular resistance, muscle capillary density and mitochondrial function), while V'_E/V'_{CO_2} and P_{ETCO_2} are more directly related to ventilation [22]. However, in this selected population of healthy subjects, predictive value of peak V'_{O_2} might have also been influenced by a subject's normal fitness.

Clinical implementation of our findings relates mostly to the utility of resting P_{ETCO_2}. Though V'_E/V'_{CO_2} slope showed excellent predictive value for PPC, the overall cost-effectiveness of performing CPET in this otherwise healthy population with normal lung function seems very low. Instead, we propose routine use of P_{ETCO_2} in patients with normal lung functions scheduled for thoracotomy since this surgical procedure was the second strongest risk factor of PPC as shown by our data. Video-assisted thoracic surgery is a safer alternative to conventional thoracotomy [23]. However, in some patients, thoracotomy cannot be avoided due to known adhesions or unfavourable anatomical conditions. In these patients, resting P_{ETCO_2} might be beneficial with regard to identifying patients at risk of PPC development and requiring more intensive preoperative management (*e.g.* pulmonary prehabilitation) as PPC are associated with longer hospital LOS and costs [16, 24].

Limitations of this study include: 1) small numbers of patients with PPC in the subgroup of subjects with normal lung functions; however, this is consistent with a low risk population; 2) patients were recruited based on values of ppo-peak V'_{O_2} $\geqslant 10\ mL\cdot kg^{-1}\cdot min^{-1}$ (thus meeting the valid ERS criteria for resectability), and so preselection bias might be introduced; and 3) this subgroup analysis contained only data from healthier subjects with normal lung function (FEV_1 and D_{LCO} $\geqslant$80%), suggesting the findings and observed cut-offs of resting P_{ETCO_2} and V'_E/V'_{CO_2} slope are not generalisable to non-selected populations and remain limited solely to this subgroup of healthier patients.

We conclude that V'_E/V'_{CO_2} slope and resting P_{ETCO_2} bring incremental information regarding risk of PPC development in patients with normal values of FEV_1 and D_{LCO} prior to thoracic surgery. We propose that routine resting capnography (P_{ETCO_2} measurement) be performed in addition to spirometry and D_{LCO} assessment for patients scheduled for lung resection *via* thoracotomy.

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The study was registered at www.ClinicalTrials.gov with identifier number NCT03498352. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics: The study was conducted in accordance with the declaration of Helsinki and approved by the local Ethics Committee of St Anne's University Hospital in Brno (reference number 19JS/2017, date of approval 12 April 2017; reference number 2G/2018, date of approval 21 March 2018) and by the local Ethics Committee of the University Hospital Brno (reference number 150617/EK, date of approval 19 June 2017). All participants signed written informed consent. The manuscript adheres to the applicable STROBE guidelines for observational studies.

Consent for publication: Not applicable.

Author contributions: All authors contributed to the data collection, analysis and interpretation, and writing of the manuscript. I. Cundrle Jr, K. Brat and L.J. Olson designed the study. I. Cundrle Jr registered the CMRD project at ClinicalTrials.gov. I. Cundrle Jr and K. Brat secured funding for the research project. I. Cundrle Jr, K. Brat, M. Bratova, Z. Merta, P. Homolka, L. Mitas, V. Sramek and Z. Chovanec collected the data within both centres. K. Brat and I. Cundrle Jr designed the analyses for this particular study. M. Svoboda performed the statistical analysis. K. Brat, M. Svoboda and I. Cundrle Jr drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final submitted version.

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References

1 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.
2 Agostini P, Cieslik H, Rathinam S, *et al.* Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? *Thorax* 2010; 65: 815–818.
3 Boffa DJ, Allen MS, Grab JD, *et al.* Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. *J Thorac Cardiovasc Surg* 2008; 135: 247–254.
4 Powell HA, Tata LJ, Baldwin DR, *et al.* Early mortality after surgical resection for lung cancer: an analysis of the English National Lung cancer audit. *Thorax* 2013; 68: 826–834.
5 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: 1725–1730.
6 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: 1263–1270.
7 Sandblom G, Videhult P, Crona Guterstam Y, *et al.* Mortality after a cholecystectomy: a population-based study. *HPB (Oxford)* 2015; 17: 239–243.
8 Humes DJ, Simpson J. Acute appendicitis. *BMJ* 2006; 333: 530–534.
9 Brunelli A, Belardinelli R, Pompili C, *et al.* Minute ventilation-to-carbon dioxide output (V'_E/V'_{CO_2}) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *Ann Thorac Surg* 2012; 93: 1802–1806.
10 Shafiek H, Valera JL, Togores B, *et al.* Risk of postoperative complications in chronic obstructive lung diseases patients considered fit for lung cancer surgery: beyond oxygen consumption. *Eur J Cardiothorac Surg* 2016; 50: 772–779.
11 Brat K, Homolka P, Merta Z, *et al.* Prediction of postoperative complications: ventilatory efficiency and rest end-tidal carbon dioxide. *Ann Thorac Surg* 2022; in press [https://doi.org/10.1016/j.athoracsur.2021.11.073].
12 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: 269–272.
13 Miller MR, Crapo R, Hankinson J, *et al.* General considerations for lung function testing. *Eur Respir J* 2005; 26: 153–161.
14 Torchio R, Guglielmo M, Giardino R, *et al.* Exercise ventilatory inefficiency and mortality in patients with chronic obstructive pulmonary disease undergoing surgery for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2010; 38: 14–19.

15 Choi H, Mazzone P. Preoperative evaluation of the patient with lung cancer being considered for lung resection. *Curr Opin Anaesthesiol* 2015; 28: 18–25.
16 Sanchez-Lorente D, Navarro-Ripoll R, Guzman R, *et al.* Prehabilitation in thoracic surgery. *J Thorac Dis* 2018; 10: Suppl. 22, S2593–S2600.
17 Miyazaki T, Callister MEJ, Franks K, *et al.* Minute ventilation-to-carbon dioxide slope is associated with postoperative survival after anatomical lung resection. *Lung Cancer* 2018; 125: 218–222.
18 Woods PR, Olson TP, Frantz RP, *et al.* Causes of breathing inefficiency during exercise in heart failure. *J Card Fail* 2010; 16: 835–842.
19 Lewis DA, Sietsema KE, Casaburi R, *et al.* Inaccuracy of noninvasive estimates of VD/VT in clinical exercise testing. *Chest* 1994; 106: 1476–1480.
20 Cundrle I, Johnson BD, Rea RF, *et al.* Modulation of ventilatory reflex control by cardiac resynchronization therapy. *J Card Fail* 2015; 21: 367–373.
21 Cundrle I Jr, Somers VK, Johnson BD, *et al.* Exercise end-tidal CO_2 predicts central sleep apnea in patients with heart failure. *Chest* 2015; 147: 1566–1573.
22 Bassett DR Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc* 2000; 32: 70–84.
23 Oparka J, Yan TD, Ryan E, *et al.* Does video-assisted thoracic surgery provide a safe alternative to conventional techniques in patients with limited pulmonary function who are otherwise suitable for lung resection? *Interact Cardiovasc Thorac Surg* 2013; 17: 159–162.
24 Gravier FE, Smondack P, Boujibar F, *et al.* Prehabilitation sessions can be provided more frequently in a shortened regimen with similar or better efficacy in people with non-small cell lung cancer: a randomised trial. *J Physiother* 2022; 68: 43–50.