Minute ventilation to carbon dioxide output (V'_E/V'_{CO2} slope) is the strongest death predictor before larger lung resections

Roberto Torchio[1], Alessandra Mazzucco[2], Marco Guglielmo[1], Roberto Giardino[2], Francesco Ardissone[2], Claudio Ciacco[1]

[1] Respiratory Function and Sleep Laboratory, AOU San Luigi, Orbassano (TO)
[2] Thoracic Surgery, University of Turin, AOU San Luigi Orbassano (TO), Italy

Abstract

The minute ventilation to carbon dioxide (CO_2) production ratio (V'_E/V'_{CO2} slope) was recently identified as a mortality predictor after lung surgery, but the effect of the resection extent was not taken into account. The aim of this study was to investigate the role of V'_E/V'_{CO2} slope as preoperative mortality predictor depending on the type of surgery performed. Retrospective analysis was performed on 263 consecutive patients evaluated before surgery for lung cancer. Death within 30 days and serious respiratory complications were considered. Univariate and multivariate regression analyses were used to identify independent predictors of death. Lobectomy or bilobectomy were performed in 186 patients with 29/186 (15.6%) serious pulmonary complications and 6/186 (3.2%) deaths. Pneumonectomy was performed in 77 patients with 14/77 (18.2%) serious complications and 5/77 (6.5%) deaths. Considering the whole group, the peak oxygen consumption ($V'_{O2peak,}$ L/min; z=-2.66, p<0.008, OR 0.007) and V'_E/V'_{CO2} slope (z=2.80, p<0.005, OR 1.14) were independent predictors of mortality whereas in pneumonectomies V'_E/V'_{CO2} slope (z=2.34, p<0.02, OR 1.22) was the only independent predictor of mortality. High V'_E/V'_{CO2} slope, age and low V'_{O2peak} are predictors of death and severe complications after lung surgery. Before larger resections as pneumonectomies an increased V'_E/V'_{CO2} slope represents the best mortality predictor.

Corresponding author: Dr. Roberto Torchio, SSD Laboratorio Fisiopatologia Respiratoria e Centro Disturbi Respiratori nel Sonno, Dipartimento Fisiopatologia Cardio-Respiratoria, AOU San Luigi, Regione Gonzole 10, 10043 Orbassano (TO), Italy.
Fax: +39.011.9026488. E-mail: r.torchio@inrete.it

Key words: Pneumonectomy; lung cancer; V'_E/V'_{CO2} slope.

Authors' contributions: RT, FA, conception and design of research; RT, MG, CC, performed functional respiratory studies; RG, FA, AM, performed surgical procedures; RT, AM, analyzed data; RT, MG, CC, AM, FA, interpreted results of the study; RT, AM, edited and revised the manuscript; all authors approved the final version of manuscript.

Conflict of interest: the authors declare that no potential conflicts of interest exist with any companies and/or organizations whose products or services may be discussed in this article.

Received for publication: 7 March 2017
Accepted for publication: 26 August 2017

Tipografia PI-ME Editrice, Italy
Monaldi Archives for Chest Disease 2017; 87:817
doi: 10.4081/monaldi.2017.817

Introduction

The assessment of the lower limit of surgical tolerance for lung resection in patients with non-small-cell lung cancer (NSCLC) remains difficult [1-6]. Although peak oxygen consumption (V'_{O2peak}) is the most used variable in the preoperative evaluation before lung resection, recently the ventilatory inefficiency (measured as the minute ventilation to CO_2 production ratio (V'_E/V'_{CO2} slope) was considered as useful [7], or even the best [8] survival predictor after lung resection. Unfortunately, differences in extension of resection were not taken into account. The aim of this study was to investigate the role of V'_E/V'_{CO2} slope as a preoperative mortality and morbidity predictor depending on type of surgery performed (pneumonectomy or lobectomy/bilobectomy).

Materials and Methods

This is a retrospective review of a database including 263 consecutive patients with lung cancer, referred for pre-operative evaluation between 2005 and 2013, that performed a cardiopulmonary exercise test (CPET) before surgery because they had higher operative risk according to an algorithm proposed in 2009 by the European Respiratory Society/European Society of Thoracic Surgeons (ERS/ESTS) [5] [CPET was recommended in patients with bronchial obstruction and/or reduced pulmonary diffusion capacity for carbon monoxide ($D_{,LCO}$)]. This algorithm was amended in some way by the ACCP recommendations in 2013 [6] to reduce the number of unnecessary CPET but for the present study only the 2009 ERS/ESTS recommendations were considered.

The operability was evaluated by means of standard clinical, radiographic (conventional and computed tomographic), bronchoscopic, and staging procedures (mediastinoscopy or mediastinotomy), as appropriate [5,6]. The anesthesiologic procedure included single lung ventilation using a double-lumen endobronchial tube. Operations were performed by dedicated thoracic surgeons. All the patients gave their informed consent to the surgical procedure according to Institutional Ethical Committee.

Anatomic lung resections with systematic pulmonary and mediastinal lymphadenectomy were performed through a lateral muscle-sparing thoracotomy. Standard post-operative management included anti-thrombotic prophylaxis, chest pain control using combinations of epidural (or paravertebral) analgesia and parenteral or oral pain relieving drugs as necessary, chest physiotherapy and mobilization as early as possible.

Preoperative cardio-pulmonary function tests

Spirometry and lung diffusion capacity

Spirometry, flow-volume curves, and absolute lung volumes were obtained using a plethysmograph (Autobox, Sensomedics, Yorba Linda, CA, USA). The lung diffusion capacity for carbon monoxide (D_L,co) was determined with the same equipment, using a standard single breath technique and the final result was obtained considering the mean of two acceptable measures obtained at intervals of at least 4 min. Predicted values for spirometry, lung volumes and D_L,co were taken from Quanjer *et al.* [9].

Cardiopulmonary exercise testing

Patients underwent symptom-limited CPET with a respiratory gas exchange measurement, using a treadmill with Balke protocol [10]. A 12-lead electrocardiogram, heart rate, and arterial blood pressure were obtained at rest and at each min during exercise.

For breath-by-breath gas exchange measurements, a Sensor Medics Vmax 29C system (Sensormedics) was used. Minute ventilation [V'_E, BTPS (Body Temperature, atmospheric Pressure Saturated with water vapour)], peak oxygen uptake [V'_{O2peak}, STPD (Standard Temperature and Pressure Dry)], carbon dioxide output (V'_{CO2}, STPD), were calculated breath-by-breath. The V'_E/V'_{CO2} slope was measured by linear regression, excluding the non-linear part of the data after the onset of ventilatory compensation for metabolic acidosis [10], predicted for V'_E/V'_{CO2} slope were from Sun *et al.* [11].

V'_{O2peak} was defined as the highest 20-second average value obtained during the last stage of the exercise test [10]. Predicted values were derived according Jones [12].

Predicted post-operative values

Predicted post-operative ($_{ppo}$) values were obtained according to ERS/ESTS clinical guidelines [5,13] using preoperative pulmonary function data with information on the number of bronchopulmonary segments removed (for lobectomy) or fraction of total perfusion for the lung to be resected (for pneumonectomy) using preoperative radiologic studies).

For illustrative purposes, the formulas below are used for estimation of FEV_1 ($_{ppo}$) and the same equations can be used to estimate the D_LCO ($_{ppo}$):

Pneumonectomy (using the perfusion method)
FEV_1 ($_{ppo}$) = preoperative FEV_1 x (1 - fraction of total perfusion for the lung to be resected)

Lobectomy (using the anatomic method)
FEV_1 ($_{ppo}$) = preoperative FEV_1 x (1 - a/b)

Where a is the number of unobstructed segments to be resected; and b is the total number of unobstructed segments. The preoperative FEV 1 is taken as the best measured postbronchodilator value.

Mortality and morbidity

The operative mortality was defined as death by whatever cause within 30 days after surgery [4,6].

According to the Literature, major cardiopulmonary morbidity occurred if one or more than one of the following were present: cardiac failure requiring inotropic support other than renal dose dopamine; hemodinamically unstable arrhythmia requiring treatment; pulmonary embolism diagnosed by high probability perfusion scan or helical computed tomographic scan; respiratory failure (partial arterial oxygen pressure (P_aO_2) <65 mm Hg and/or partial arterial carbon dioxide pressure (P_aCO_2) >45 mmHg) requiring non-invasive or invasive mechanical ventilation; pneumonia defined by typical clinical, laboratory, and radiographic features; atelectasis requiring bronchoscopy and/or non-invasive assisted ventilation [4,6].

Statistical analysis

Data are reported as means and standard deviations. For respiratory parameters absolute and percent of the predicted values were considered. Differences between the groups were tested for significance by Student's *t*-test. Values of $p<0.05$ were considered statistically significant.

Multiple logistic regression analysis was performed to identify independent predictors of post-operative death and post-operative complications using age, body mass index (BMI), spirometric and exercise cardio-respiratory parameters as potential outcome predictors. The best model was selected with step-wise approach using alpha value of 0.05 to include and 0.10 to remove variables. Analysis was performed using Stata 10 statistical package (Stata corporation, LP, College Station, TX, USA).

From the best model the Receiver Operating Characteristic (ROC) curve for age, V'_{O2peak} and V'_E/V'_{CO2} slope in predicting death was estimated and the area under the curve calculated with the Stata post-estimation procedure (lroc).

The results of single variables logistic regression analyses were also reported.

Results

The population included 212 (80,6%) males and 51 (19,4%) females average age 65±8 years. Nineteen (7%) were no-smokers, 113 (43%) ex-smokers and 131 (50%) were active smokers. Nine patients (0.3%) had induction chemotherapy. None had Video-Assisted Thoracic Surgery.

One hundred and eighty-six lobectomies/bilobectomies and 77 pneumonectomies were performed. In Table 1 a description of severe complications occurred is reported with subdivision according to the surgery type performed. Forty-three patients (16.3%) suffered severe cardio-respiratory complications: 29/186 patients (15.6%) after lobectomy/bilobectomy and 14/77 (18.2%) after pneumonectomy. These data were similar to previously reported by other authors [2,3,6].

Eleven patients (4.2%) died within 30 days after surgery (Table 1). Six out of 186 patients died after lobectomy/bilobectomy (3.2%) and 5 after pneumonectomy (6.5%). Seven out of these patients showed, after initial hypoxemic respiratory failure, clinical signs of acute heart failure. Two of these eleven patients died for ARDS and 2 for septic shock and Multiple Organ Failure.

Forty-three patients (16.3%) showed severe postoperative complications: 29 patients after lobectomy/bilobectomy (15.6%) and 14 after pneumonectomy (18.2%).

Differences in functional parameters between survivor or non-survivor patients are reported in Table 2. Age, ${}_{ppo}$DLCO, V'_{O2peak} and ${}_{ppo}V'_{O2peak}$ (expressed as L/min, or %predicted or as mL/min/kg), and V'_E/V'_{CO2} slope (absolute value or % predicted) are the parameters which were significantly different. The data clearly shows that non-survivors are older and presented worse cardiopulmonary performance.

Differences in functional parameters between patients with or without severe cardio-pulmonary complications are reported in Table 3: ${}_{ppo}FEV_1$ (%predicted), DLCO and ${}_{ppo}$DLCO, V'_{O2peak} and ${}_{ppo}V'_{O2peak}$ (expressed as L/min, or %predicted or mL/min/kg), and V'_E/V'_{CO2} slope (absolute value or %predicted) are the parameters significantly different.

In Table 4 are reported data on functional parameters between survivors and non-survivors in patients that underwent lobectomy/bilobectomy or pneumonectomy.

Between lobectomies/bilobectomies age, V'_{O2peak} (L/min and %predicted), ${}_{ppo}V'_{O2peak}$ (L/min) and V'_E/V'_{CO2} slope (absolute value) are the only parameters significantly different between survivors and non-survivors.

On the other hand, V'_{O2peak} (L/min), ${}_{ppo}V'_{O2peak}$ (L/min) and V'_E/V'_{CO2} slope (absolute value or % predicted) are the only parameters significantly different in pneumonectomy survivors and non survivors. One consideration must be taken into account. Patients that underwent lobectomy/bilobectomy were younger than patients that received pneumonectomy (61±9 *vs* 65±7 years; p<0.01) so the predicted post-operative cardio-respiratory parameters were obviously lower in pneumonectomy group.

Considering severe post-operative cardiopulmonary complications in the whole group a logistic regression analysis identified the V'_{O2peak} (L/min) (z=-2.25, p<0.025, Odd Ratio 0.203) and V'_E/V'_{CO2} slope (z=2.04, p<0.04, Odd Ratio 1.06) as the best predictors of severe cardiopulmonary post-operative complications. The same test (Table 5) also identified V'_{O2peak} (L/min) (z=-2.66, p<0.008, OR 0.0073 and, V'_E/V'_{CO2} slope (z=2.80, p<0.005, OR 1.14) as an independent predictor of mortality.

Analyzing the surgery type, the logistic regression analysis identified V'_{O2peak} (L/min) (z=-2.21, p<0.027, OR 0.0011), V'_E/V'_{CO2} slope (z=2.89,

Table 1. Severe cardiopulmonary complications after lung resection (for definition of complications see text).

Post-operative complications	Total	Lobectomy / bilobectomy	Pneumonectomy
Number of patients	263	186	77
Non-survivors (% of total)	11 (4.2%)	6 (3.2%)	5 (6.5%)
Total complications (% of total)	43 (16.3%)	29 (15.6%)	14 (18.2%)
Respiratory failure (P_aO_2 <65 mm Hg and/or P_aCO_2 > 45 mm Hg) requiring invasive or not invasive mechanical ventilation	15 (5.7%)	9 (4.8%)	6 (7.7%)
Hemodinamically unstable arrhythmia requiring treatment	4 (1.5%)	3(1.6%)	1(1.3%)
Pneumonia (temperature >38°C and purulent sputum and infiltrate on radiography)	4 (1.5%)	3(1.6%)	1(1.3%)
Pulmonary embolism (high probability on ventilation perfusion scan or angiogram)	0	0	0
Lobar atelectasis (needing bronchoscopy)	9 (3.4%)	8(4.3%)	1(1.3%)

P_aO_2, partial arterial oxygen pressure; P_aCO_2, partial arterial carbon dioxide pressure.

Table 2. Demographic, spirometric and cardiopulmonary exercise test data (mean ± SD) in the total population, survivors and non-survivors.

		Total	Survivors	Non-survivors
Number		263	252	11
Age (years)		65.2 ± 7.8	65.0 ± 7.9	69.9 ± 4.1*
BMI (Kg/m²)		26.1 ± 4.3	26.2 ± 4.3	23.6 ± 4.0
Gender (M/F)		212/51	204/48	8/3
FEV_1 (%pred)		77.6 ± 18.8	77.3 ± 18.9	82.8 ± 16.9
FEV_1/VC (%pred)		81.6 ± 14.0	81.4 ± 14.0	85.3 ± 11.7
${}_{ppo}FEV_1$ (%pred)		55.5 ± 17.0	55.4 ± 16.9	55.7 ± 18.4
D_LCO % (%pred)		68.5 ± 18.8	68.8 ± 18.9	60.0 ± 15.1
${}_{ppo}D_LCO$ (%pred)		48.9 ± 15.7	49.3 ± 15.8	38.4 ± 11.1*
V'_{O2peak}	(L/min)	1.39 ± 0.33	1.40 ± 0.33	1.04 ± 0.16***
	(%pred)	66.1 ± 16.3	66.6 ± 16.4	53.2 ± 8.7**
	mL/min/Kg)	19.0 ± 3.4	19.1 ± 3.4	16.9 ± 2.4*
${}_{ppo}V'_{O2peak}$	(L/min)	0.99 ± 0.31	1.0 ± 0.3	0.7 ± 0.2***
	(mL/min/Kg)	13.7 ± 3.6	13.8 ± 3.6	11.3 ± 2.8*
V'_E/V'_{CO2} slope		31.1 ± 6.0	30.8 ± 5.7	38.4 ± 8.1***
V'_E/V'_{CO2} slope (%pred)		118.0 ± 22.8	117.0 ± 21.8	143.2 ± 32.5***

BMI, Body mass index; FEV_1, forced expiratory ventilation in 1 s; D_LCO, carbon monoxide transfer capacity; VC, vital capacity; ${}_{ppo}$, post-operative predicted value; V'_E/V'_{CO2} slope: slope of the ratio between minute ventilation (V'_E) and carbon dioxide output (V'_{CO2}) during exercise; V'_{O2peak}, maximal oxygen uptake at peak of exercise; *p<0.05; **p<0.005; ***p<0.001.

Table 3. Demographic, spirometric and cardiopulmonary exercise test data in patients with or without post-operative complications (mean + SD).

		No severe complications	Severe complications
Number		220	43
Age (years)		65.0 ± 7.9	66.1 ± 7.7
BMI (Kg/m²)		26.0 ± 4.1	26.5 ± 5.2
Gender (M/F)		180/40	32/11
FEV_1 (%pred)		78.3 ± 18.6	73.8 ± 19.8
FEV_1/VC (%pred)		81.8 ± 13.7	80.3 ± 15.1
$_{ppo}FEV_1$ (%pred)		56.4 ± 17.0	50.6 ± 16.2*
D_LCO % (%pred)		69.7 ± 19.1	61.5 ± 16.3*
$_{ppo}D_LCO$ (%pred)		50.0 ± 16.1	42.6 ± 12.1**
V'_{O2peak}	(L/min)	1.4 ± 0.3	1.2 ± 0.3***
	(%pred)	67.3 ± 16.6	59.8 ± 13.5**
	mL/min/Kg)	19.3 ± 3.4	17.5 ± 2.6***
$_{ppo}V'_{O2peak}$	(L/min)	1.02 ± 0.3	0.88 ± 0.21***
	(mL/min/Kg)	14.0 ± 3.7	12.2 ± 2.8*
V'_E/V'_{CO2} slope		32.7 ± 5.7	33.1 ± 7.7*
$V'E/V'_{CO2}$ slope (%pred)		116.7 ± 21.5	125.0 ± 28.2*

BMI, Body mass index; D_LCO, carbon monoxide transfer capacity; FEV_1, forced expiratory ventilation in 1 s; VC, vital capacity; $_{ppo}$, post-operative predicted value; V'_E/V'_{CO2} slope: slope of the ratio between minute ventilation (V'_E) and carbon dioxide output (V'_{CO2}) during exercise; V'_{O2peak}, maximal oxygen uptake at peak of exercise; *p<0.05; **p<0.005; ***p<0.001.

p<0.004, OR 1.14) as independent predictors of mortality in patients who underwent lobectomy or bilobectomy, whereas in patients who underwent pneumonectomy the V'_E/V'_{CO2} slope (z=2.34, p<0.02, OR 1.22) was the only independent predictor of mortality.

In these patients, the Receiver Operating Characteristic (ROC) curve for V_E/V'_{CO2} slope sensitivity and specificity in predicting postoperative death was calculated. The area under ROC curve was 0.894 (95% confidence interval 0.70-1.01), with a good model prediction capacity. No significant effect was detected for COPD severity in the multivariate final model. No deaths occurred when the V'_E/V'_{CO2} slope, was in the normal range. The association between a high V'_E/V'_{CO2} slope and the risk of death was present also after all the patients with peak V'_{O2} <15 mL/kg/min were excluded.

Table 5. Logistic regression analysis results (the best fitted model is reported) of risk of death, on the total number of patients and on patients that underwent pneumonectomy, as dependent variable.

	Odds ratio	95% Confidence interval	z	p>z
Total				
V'_E/V'_{CO2} slope	1.14	1.04-1.25	2.80	0.005
V'_{O2peak}	0.0073	0.0002-0.272	-2.66	0.008
Pneumonectomy				
V'_E/V'_{CO2} slope	1.22	1.03-1.45	2.34	0.02
V'_{O2peak}	0.032	0.0002-4.67	-1.35	0.177

V'_E/V'_{CO2} slope, slope of the ratio between minute ventilation (V'_E) and carbon dioxide output (V'_{CO2}) during exercise; V'_{O2peak}, maximal oxygen uptake at peak of exercise (L/min).

Table 4. Demographic, spirometric and cardiopulmonary exercise test data (mean ± SD) in the total population, survivors and non-survivors.

Number		Lobectomy/bilobectomy 186		Pneumonectomy 77	
		Survivors	Not survivors	Survivors	Not survivors
Number		180	6	72	5
Age (years)		65.6 ± 7.4	72.7 ± 1.9*	63.4 ± 8.9	66.6 ± 3.6
BMI (Kg/m²)		26.1 ± 4.2	23.1 ± 3.9	26.4 ± 4.6	24.3 ± 4.6
Gender (M/F)		145/35	05/01	59/13	03/02
FEV_1 (%pred)		76.7 ± 20.1	82.2 ± 19.2	78.8 ± 15.7	83.5 ± 15.9
FEV_1/VC (%pred)		80.3 ± 14.5	80.9 ± 9.3	84.3 ± 12.6	90.5 ± 13.1
$_{ppo}FEV_1$ %pred)		61.3 ± 15.9	66.7 ± 17.5	40.8 ± 8.8	42.5 ± 8.1
D_LCO % %pred)		67.5 ± 18.4	55.8 ± 18.1	72.0 ± 20.1	64.2 ± 11.8
$_{ppo}D_LCO$ (%pred)		53.9 ± 15.4	44.2 ± 12.7	37.5 ± 9.3	32.7 ± 6.0
V'_{O2peak}	(L/min)	1.39 ± 0.32	1.00 ± 0,15**	1.42 ± 0.36	1.08 ± 0,19*
	(%pred)	66.7 ± 15.9	53.7 ± 8.4*	66.4 ± 17.6	52.6 ± 10.0
	mL/min/Kg)	19.1 ± 3.4	16.7 ± 1.6	19.3 ± 3.2	17.2 ± 3.3
$_{ppo}V'_{O2peak}$	(L/min)	1.11 ± 0.28	0.81 ± 0.14**	0.74 ± 0.19	0.56 ± 0.11*
	(mL/min/Kg)	15.3 ± 3.1	13.4 ± 1.2	10.0 ± 1.7	8.8 ± 2.0
V'_E/V'_{CO2} slope		30.8 ± 5.9	36.0 ± 4.3*	30.8 ± 5.3	41.3 ± 11,0***
V'_E/V'_{CO2} slope (%pred)		116.6 ± 22.3	132.4 ± 16.1	117.9 ± 20.6	156.1 ± 44.0***

BMI, Body mass index; D_LCO, carbon monoxide transfer capacity; FEV_1, forced expiratory ventilation in 1 s; VC, vital capacity; $_{ppo}$, post-operative predicted value; V'_E/V'_{CO2} slope: slope of the ratio between minute ventilation (V'_E) and carbon dioxide output (V'_{CO2}) during exercise; V'_{O2peak}, maximal oxygen uptake at peak of exercise; *p<0.05; **p<0.005; ***p<0.001 between survivors and non-survivors.

Discussion

The main results of this study may be summarized as follows: i) V'_{O2peak} with V'_E/V'_{CO2} slope, as previously reported [7,8], are good predictors of occurrence of severe postoperative cardiopulmonary complications after lung resection in patients considered operable after a preoperative study including CPET; ii) an high V'_E/V'_{CO2} slope can be considered an independent postoperative mortality predictor only before pneumonectomy; iii) no deaths occurred when the V'_E/V'_{CO2} slope was in the normal range.

The use of exercise testing in the preoperative evaluation of patients with impaired lung mechanics and gas exchange is safe and simple and the V'_{O2peak} was the first exercise testing variable recognized as prognostic in many clinical situations, from the preoperative evaluation before lung resection [1,4], to CHF patients' management [14-17]. Moreover, between cardiopulmonary exercise test parameters, the V'_E/V'_{CO2} slope measurement had clinical relevance in patients with pulmonary congestion and heart failure [18,19] and was recognized as a marker of pulmonary hypertension in COPD patients [20].

Although the V'_{O2peak} is the most used variable in the preoperative evaluation before lung resection, recently the ventilatory inefficiency, measured as the minute ventilation to CO_2 production ratio (V'_E/V'_{CO2} slope) was considered a useful [7] or even the best [8] survival predictor after lung resection. The V'_E/V'_{CO2} slope was repeatedly identified as a strong and independent prognostic survival index in CHF patients with mild-to-moderate exercise limitation. Most of the studies in CHF patients reported that the V'_E/V'_{CO2} slope was prognostically superior to V'_{O2peak} [15,16], which underscores the clinical importance of ventilatory inefficiency. Unfortunately, in the past literature on the preoperative evaluation in thoracic surgery, the effects of resection extension were not taken into account. The reduction of the vascular bed after lung resection can worsen pulmonary hemodynamics, especially in patients with pre-existing sub-clinical pulmonary hypertension or latent heart failure. It seems to be possible that COPD non-survivor patients with high V'_E/V'_{CO2} slope might have worse hemodynamics, with sub-clinical pulmonary congestion [18], heart failure or pulmonary hypertension. Lung resection could stress this situation, promoting acute cardiopulmonary failure, that represents the main cause of death in these patients. This fact can be more important when a greater reduction in vascular pulmonary bed occurs as in pneumonectomy and so in this way high V'_E/V'_{CO2} slope could predict an unfavorable outcome.

V'_{O2peak} is influenced by the contribution of the heart, lungs, oxygen transport system, and skeletal muscles to external work. So, it can represent a more global variable than V'_E/V'_{CO2} slope alone, which is specifically the expression of ventilatory efficiency. In this regard, the V'_E/V'_{CO2} slope could improve risk-stratification independently of the V'_{O2peak}.

In our population the V'_{O2peak} is a better predictor of survival if expressed as absolute value (liters per minute) than if expressed in mL/Kg/min or % predicted. This finding suggests that caution should be taken when analyzing preoperative data in patients with low BMI. In these patients, when the V'_{O2peak} is expressed as mL/kg/min, the lower the weight, the higher is the V'_{O2peak} (mL/min/Kg), causing a potential misleading interpretation of the cardiopulmonary performance. Furthermore, in the preoperative evaluation it must be considered that patients with low weight and BMI have worse outcomes [21].

This study has some limitations. Firstly, its retrospective nature potentially introduces patients' selection biases. In fact, the data is retrospectively analyzed on a set of patients considered operable according to criteria previously validated, that did not consider ventilation inefficiency. Secondly, although this population was relatively large, the absolute number of non-survivors, especially among patients where pneumonectomy was performed, was low reducing the reliability of statistical inferences. Larger number of non-survivors however could improve analysis but especially if the values were not statistically significant and this was not the case. For these reasons, in preoperative evaluation of lung resections of different extensions, differences of predictivity of ventilator inefficiency should be tested in further larger series of patients with a prospective approach.

In conclusion, high V'_E/V'_{CO2} slope, age and low V'_{O2peak} are predictors of death and severe complications after lung surgery. Before larger resections as pneumonectomies an increased V'_E/V'_{CO2} slope represents the best mortality predictor and in our patients no deaths occurred when the V'_E/V'_{CO2} slope was in the normal range. Particularly in COPD patients an increase in the V'_E/V'_{CO2} slope can be considered a marker of pulmonary hypertension or subclinical heart failure and in this case these patients must be carefully screened before surgical procedures with large parenchymal exeresis can take place.

References

1. Bolliger CT, Jordan P, Solèr M, et al. Exercise capacity as a predictor of postoperative complications in lung resection candidates. Am J Respir Crit Care Med 1995;151:1472-80.
2. Bolliger CT, Wyser C, Roser H, et al. Lung scanning and exercise testing for the prediction of postoperative performance in lung resection candidates at increased risk for complications. Chest 1995;108:41-8.
3. Pate P, Tenholder MF, Griffin JP, et al. Preoperative assessment of the high-risk patient for lung resection. Ann Thorac Surg 1996;61:1494-500.
4. Brutsche MH, Spiliopoulos A, Bolliger CT, et al. Exercise capacity and extent of resection as predictors of surgical risk in lung cancer. Eur Respir J 2000;15: 828-32.
5. 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.
6. 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.
7. 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;38:14-20.
8. 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.
9. Quanjer PH, Tammeling GJ, Cotes JE, et al. Symbols, abbreviations and units. Working party standardization of lung function tests. European Community for Steel and Coal. Eur Respir J 1993;(Suppl. 16):85-100.
10. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;16:211-77.
11. Sun XG, Hansen JE, Garatachea N, et al. Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med 2002; 166:1443-18.
12. Jones NL. Clinical exercise testing, 4 ed. WB Saunders, Philadelphia; 1997.

13. Bolliger CT, Guckel C, Engel H, et al. Prediction of functional reserves after lung resection: comparison between quantitative computed tomography, scintigraphy, and anatomy. Respiration 2002;69:482-9.
14. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. Circulation 1997;96: 2221-7.
15. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilator response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation 2001;103:967-72.
16. Poole-Wilson PA, Coats AJ. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 1997;29:585-90.
17. Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 1997;29:1585-90.
18. Malfatto G, Caravita S, Giglio A, et al. Pulmonary congestion at rest and abnormal ventilation during exercise in chronic systolic heart failure. J Am Heart Assoc 2015;5:1-8.
19. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. Circulation 2007;115:2410-7.
20. Holverda S, Bogaard HJ, Groepenhoff H, et al. Cardiopulmonary exercise test characteristics in patients with chronic obstructive pulmonary disease and associated pulmonary hypertension. Respiration 2008;76:160-7.
21. Ferguson MK, Im HK, Watson S, et al. Association of body mass index and outcomes after major lung resection. Eur J Cardiothorac Surg 2014; 45:e94-e99.