Exercise ventilatory inefficiency and mortality in patients with chronic obstructive pulmonary disease undergoing surgery for non-small-cell lung cancer

Roberto Torchio a,*, Marco Guglielmo a, Roberto Giardino b, Francesco Ardissone b, Claudio Ciacco a, Carlo Gulotta c, Aleksandar Veljkovic d, Massimiliano Bugiani e

a SSD Laboratorio di Fisiopatologia Respiratoria e Centro del Sonno, AOU San Luigi Orbassano, Torino, Italy
b SCDO Chirurgia Toracica, Universita Degli Studi Di Torino, AOU San Luigi Orbassano, Torino, Italy
c SCDO Malattie Apparato Respiratorio 1 AOU San Luigi Orbassano Torino, Italy
d Scuola Specializzazione Malattie Apparato Respiratorio Universita di Torino, Torino, Italy
e SCDO Pneumologia CPA-ASL02 Torino, Torino, Italy

Received 5 October 2009; received in revised form 6 January 2010; accepted 12 January 2010; Available online 30 March 2010

Abstract

Objective: Surgical resection is the treatment of choice to cure patients with non-small-cell lung cancer (NSCLC); nevertheless, the assessment of the lower limit of surgical tolerance remains difficult. Ventilatory inefficiency (measured as the ventilation to CO2 production ratio (V̇e/V̇ CO2 slope) is a survival predictor in pulmonary hypertension (PH) and chronic heart failure (CHF) and is considered a marker of PH in chronic obstructive pulmonary disease (COPD). The aim of this study was to investigate the role of V̇e/V̇ CO2 slope as preoperative mortality and morbidity predictor in COPD patients submitted to lung resection for NSCLC and considered operable according to current standards. Methods: A retrospective analysis was performed in 145 consecutive COPD patients with lung cancer (128 males and 17 females), with a mean age of 64 years (range: 41–82 years) who were referred for preoperative evaluation. Because of bronchial obstruction or reduced pulmonary diffusion capacity for carbon monoxide (DLCO), all these patients were considered operable only after a cardiopulmonary exercise test showed a preserved cardiopulmonary function. Results: A total of 98 lobectomies, eight bilobectomies and 39 pneumonectomies (13 left and 26 right) were performed. Twenty-one patients (14.5%) suffered severe cardio-respiratory complications; 15/106 patients (14.2%) after lobectomy/bilobectomy and 6/39 (15.4%) after pneumonectomy (5.1%). Considering all functional parameters before surgery and the postoperative predicted values, a logistic regression analysis indviduated the V̇e/V̇ CO2 slope as the only independent mortality predictor (odds ratio (OR): 1.24 z = 2.77; p < 0.007). The V̇ O2 peak was instead the best predictor for the occurrence of severe cardiopulmonary postoperative complications (OR: 0.05, z = −2.39, p < 0.02). Conclusions: In COPD patients, a high V̇e/V̇ CO2 slope before lung resection is an independent mortality predictor even in the presence of an acceptable cardiopulmonary performance. COPD patients with high V̇e/V̇ CO2 slope before surgery must be carefully screened to exclude pulmonary hypertension, especially before surgical procedures with large parenchymal exeresis.

© 2010 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Lung cancer; Postoperative complications; Cardiopulmonary exercise testing

1. Introduction

Complete anatomic surgical resection is the most effective therapeutic option in non-small-cell lung cancer (NSCLC) [1,2]. However, patients with concomitant chronic obstructive pulmonary disease (COPD) are at increased risk for postoperative cardiopulmonary morbidity and mortality [1,2]. In recent years [3–6], cardiopulmonary exercise testing (CPET) has become an established tool in the preoperative evaluation and risk stratification of COPD patients scheduled for NSCLC surgery. Poor exercise tolerance, assessed by low peak oxygen consumption (V̇ O2 peak), has been shown to be a reliable predictor of postoperative cardiopulmonary morbidity and mortality [3–6]. In some pathological conditions, the attention was recently focussed, not only on maximal aerobic capacity measured as V̇ O2 peak, but also on ventilatory inefficiency, measured as the total ventilation – carbon dioxide production ratio (V̇e/V̇ CO2 slope) [7–10]. Currently, the increased V̇e/V̇ CO2 slope is considered a marker of pulmonary hypertension (PH) in COPD patients [7], and it is associated with reduced survival in PH [8]. It is
also considered a reliable non-invasive prognostic predictor in chronic heart failure (CHF) patients [9]; and it was used to develop a ventilatory classification system in this disease [10].

The aim of this single-institution study was to retrospectively investigate the potential role of the slope $V'_E/V_{CO_2}$ as preoperative mortality and/or morbidity predictor in COPD patients submitted to lung resection for NSCLC and considered operable according to the current standards proposed for COPD patients by European Respiratory Society (ERS) and American Thoracic society (ATS) [5] after CPET.

2. Population

This is a retrospective review of a database including 145 out of 250 consecutive COPD patients referred for preoperative evaluation between 2005 and 2007, who performed a CPET before surgery because of a higher operative risk according to an algorithm prospectively validated and proposed under ATS—ERS standards [5, 6] (bronchial obstruction and/or reduced pulmonary diffusion capacity for carbon monoxide ($D_{L,CO}$)). In all these patients, the CPET showed a preserved cardiopulmonary function ($V'O_2_{peak} > 15$ ml kg$^{-1}$ min$^{-1}$) [5].

The population included 128 (88%) males and 17 (12%) females mean aged 64 years (range: 41—82 years). According to the ‘global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease’ (GOLD) [11] guidelines, 52 patients (36%) had mild, 84 (58%) moderate and nine (6%) severe COPD. A total of 135 patients (93%) had positive history of smoking (55—30 pack years).

Current smokers were required to quit smoking 3 weeks before surgery and before preoperative study. No patient was a smoker at the time of the surgical procedure.

Nine patients (6.2%) were treated with induction chemotherapy before surgery.

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 anaesthesiologic procedure included single-lung ventilation using a double-lumen endobronchial tube. Operations were performed by dedicated general thoracic surgeons. All patients gave informed consent to the surgical procedure. Anatomic lung resections with systematic pulmonary and mediastinal lymphadenectomy were performed through a lateral muscle-sparing thoracotomy. All patients were managed in a dedicated thoracic surgery ward. Standard postoperative management included antibiotic and antithrombotic prophylaxis, chest-pain control using combinations of epidural (or paravertebral) analgesia and parenteral or oral pain-relieving drugs as necessary and chest physiotherapy and mobilisation as early as possible.

3. Preoperative cardiopulmonary function tests

3.1. Spirometry and lung diffusion capacity

Spirometry, flow—volume curves and absolute lung volumes were obtained using a plethysmograph (Autobox, Sensodomics, Yorba Linda, CA, USA). The $D_{L,CO}$ 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. [12].

3.2. Cardiopulmonary exercise testing

Patients underwent symptom-limited CPET with a respiratory gas-exchange measurement, using a treadmill with Balke protocol [13]. A 12-lead electrocardiogram, heart rate and arterial blood pressure were obtained at rest and at each minute during exercise. For breath-by-breath gas-exchange measurements, a Sensor Medics Vmax 29C system (Sensodemics, Yorba Linda, CA, USA) was used.

Minute ventilation ($V'_E$, BTPS (body temperature, atmospheric pressure saturated with water vapour)), peak oxygen uptake ($V'O_2_{peak}$, STPD (standard temperature and pressure dry)) and carbon dioxide output ($V'CO_2$, STPD) were calculated breath-by-breath. The $V'_E/V'CO_2$ slope was measured by linear regression, excluding the non-linear part of the data after the onset of ventilatory compensation for metabolic acidosis [13]. $V'O_2_{peak}$ was considered as the highest $V'O_2$ observed during the exercise test [13]. Predictions for normal values were derived according to Jones [14].

3.3. Predicted postoperative values

Predicted postoperative values ($\text{ppo values}$) were obtained using preoperative pulmonary function testing data and information on the number of bronchopulmonary segments removed (which can usually be predicted on the basis of preoperative radiologic studies). These values were calculated as follows:

$$\text{value} = \text{preoperative value} \left(1 - \frac{\text{removed segments} \times 5.26}{100}\right).$$

We considered the lungs to have 19 segments: right upper lobe (three segments), right middle lobe (two segments), right lower lobe (five segments), left upper lobe (five segments) and left lower lobe (four segments) [15].

Only segments not totally obstructed were taken into account [2, 15].

3.4. Mortality and morbidity

The operative mortality was defined as death for whatever cause that occurred within 30 days after surgery. 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; haemodynamically unstable arrhythmia requiring treatment; pulmonary embolism diagnosed by high-probability perfusion scan or helical computed tomographic scan; adult respiratory distress syndrome; respiratory failure (partial arterial oxygen pressure ($P_aO_2$) $<65$ mmHg and/or partial arterial carbon dioxide pressure ($P_aCO_2$) $>45$ mmHg) requiring non-invasive or invasive mechanical ventilation; pneumonia defined by typical
many as 71 (48.9%) patients had histological diagnosis of squamous carcinoma, 42 (28.9%) of adenocarcinoma and 32 (22.1%) adeno-squamous or bronchiole-alveolar carcinoma. Twenty-one patients (14.5%) suffered severe cardio-respiratory complications as described in Table 1: 15/106 patients (14.2%) after lobectomy/bilobectomy and 6/39 (15.4%) after pneumonectomy. These data were similar to those previously reported by other authors [2,3,6].

Five patients (3.4%) died within 30 days after surgery (Table 2). Three out of 106 patients died after lobectomy/bilobectomy (2.8%) and two after pneumonectomy (5.1%). Three out of four of these patients showed, after initial hypoxic respiratory failure, clinical signs of acute heart failure. Clinical data of non-survivors are reported in Table 2. In four out of five of these patients, an echocardiographic study, performed within 3 months before surgery, showed a cardiac ejection fraction of 66 ± 2% and a pulmonary systolic artery pressure of 41.3 ± 13.1 mmHg.

Differences in functional parameters between survivors and non-survivors are reported in Table 3. BMI, \( V'_O2 \) peak and \( ppoFEV_1 \) (only expressed as absolute value in litres) and \( V'_E/V'_CO2 \) slope (absolute value or % predicted) are the only parameters significantly different between patient survivors and non-survivors. The \( V'_O2 \) peak (ml kg\(^{-1}\)) and \( ppoFEV_1 \) (%predicted; FEV\(_1\), forced expiratory volume in 1 s) were the only parameters significantly different (Table 4) between patients with and without severe cardio-respiratory complications.

Patients who underwent lobectomy/bilobectomy were younger than patients who received pneumonectomy (61 ± 9 vs 65 ± 7 years; \( p < 0.01 \)). The predicted postoperative cardio-respiratory parameters were obviously lower in the pneumonectomy group.

Mortality and complications were similar among patients with different histological diagnosis; the same was the case

### 4. Results

A total of 98 lobectomies, eight bilobectomies and 39 pneumonectomies (13 left and 26 right) were performed. As many as 71 (48.9%) patients had histological diagnosis of...
with patients who did or did not undergo induction chemotherapy before surgery. In severe [7] COPD patients, a higher complication rate was present (4/9 (44%) in severe COPD vs 6/52 (11.5%) and 11/84 (13%) in mild and moderate COPD respectively), but no death were observed.

The logistic regression analysis individuated the $V_{E}/V_{CO_2}$ slope as the only independent predictor of mortality (Table 5). The BMI was at the limit of statistical significance and was retained in the model because of the possibly confounding effect on prediction.

Adopting the prognostic cut-off used in CHF patients [9], and adjusting at BMI = 25 (the mean), 98% patients with $V_{E}/V_{CO_2}$ slope $< 34$ were predicted to survive, whereas 5.5% with $V_{E}/V_{CO_2}$ slope $\geq 34$ were predicted not to survive after surgery.

The ROC curve for $V_{E}/V_{CO_2}$ slope sensitivity and specificity in predicting postoperative death (Fig. 1) was calculated. The area under ROC curve was 0.871 (95% confidence interval 0.70–1.01), with a good model prediction capacity. The lower the $V_{E}/V_{CO_2}$, the better is the prognosis with respect to postoperative survival.

Considering severe postoperative cardiopulmonary complications, the $V_{O_2}$ peak (ml kg$^{-1}$ min$^{-1}$) was the best predictor of the occurrence of severe cardiopulmonary postoperative complications, decreasing the probability of complications with the increase in $V_{O_2}$ peak.

No significant effect was detected for COPD severity in the multivariate final model.

Table 4
Demographic, spirometric and cardiopulmonary exercise test data in patients with or without postoperative complications (mean ± SD), with statistical significance between the two groups.

<table>
<thead>
<tr>
<th></th>
<th>No severe complications (N = 124)</th>
<th>Severe complications (N = 21)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.7 ± 7.8</td>
<td>67.1 ± 7.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>25.4 ± 3.9</td>
<td>26.6 ± 4.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>110/14</td>
<td>18/3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV$1$ (%pred)</td>
<td>74.1 ± 15.1</td>
<td>67.6 ± 21.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV$1$/VC (%pred)</td>
<td>79.6 ± 13.6</td>
<td>82.6 ± 16.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{O_2}$ peak (l min$^{-1}$)</td>
<td>52.0 ± 14.1</td>
<td>45.8 ± 15.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{E}/V_{O_2}$ slope</td>
<td>66.7 ± 18.8</td>
<td>61.5 ± 16.8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 5
Logistic regression analysis results (the best fitted model is reported) of risk of death and risk of severe cardiopulmonary complications as dependent variables.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>$z$</th>
<th>$p &gt; z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{E}/V_{CO_2}$ slope</td>
<td>1.24</td>
<td>1.06–1.44</td>
<td>2.77</td>
<td>0.0060</td>
</tr>
<tr>
<td>BMI</td>
<td>0.75</td>
<td>0.55–1.04</td>
<td>-1.73</td>
<td>0.0830</td>
</tr>
<tr>
<td>Risk of complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{O_2}$ peak</td>
<td>0.05</td>
<td>0.01–0.58</td>
<td>-2.39</td>
<td>0.0170</td>
</tr>
<tr>
<td>BMI</td>
<td>1.17</td>
<td>1.00–1.37</td>
<td>1.97</td>
<td>0.0490</td>
</tr>
</tbody>
</table>

BMI: body mass index; $V_{E}/V_{CO_2}$ slope: the ratio between minute ventilation ($V_{E}$) and carbon dioxide output ($V_{CO_2}$) during exercise; $V_{O_2}$ peak: maximal oxygen uptake at peak of exercise.

Table 3
Demographic, spirometric and cardiopulmonary exercise test data (mean ± SD) in the total population, survivors and not survivors with statistical significance between the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Survivors</th>
<th>Not survivors</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>145</td>
<td>140</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.2 ± 7.9</td>
<td>64.0 ± 7.9</td>
<td>68.6 ± 5.4</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>25.6 ± 4.0</td>
<td>25.7 ± 3.9</td>
<td>21.6 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>128/17</td>
<td>124/16</td>
<td>4/1</td>
<td></td>
</tr>
<tr>
<td>FEV$1$ (%pred)</td>
<td>73.2 ± 16.9</td>
<td>72.9 ± 17.1</td>
<td>81.0 ± 8.3</td>
<td></td>
</tr>
<tr>
<td>FEV$1$/VC (%pred)</td>
<td>80.0 ± 14.0</td>
<td>79.7 ± 14.0</td>
<td>89.4 ± 9.9</td>
<td></td>
</tr>
<tr>
<td>$V_{O_2}$ peak (l min$^{-1}$)</td>
<td>65.9 ± 18.5</td>
<td>66.5 ± 18.5</td>
<td>50.9 ± 15.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{E}/V_{O_2}$ slope (%pred)</td>
<td>45.9 ± 13.8</td>
<td>46.3 ± 13.8</td>
<td>33.1 ± 9.5</td>
<td>&lt;0.027</td>
</tr>
<tr>
<td>$V_{E}/V_{CO_2}$ slope (%pred)</td>
<td>65.1 ± 15.6</td>
<td>65.5 ± 15.6</td>
<td>55.7 ± 13.1</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>$V_{O_2}$ peak (ml kg$^{-1}$ min$^{-1}$)</td>
<td>0.29 ± 0.29</td>
<td>0.29 ± 0.29</td>
<td>0.98 ± 0.29</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>$V_{E}/V_{CO_2}$ slope (l min$^{-1}$)</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{O_2}$ peak (l min$^{-1}$)</td>
<td>52.0 ± 14.1</td>
<td>45.8 ± 15.0</td>
<td>12.2 ± 4.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{E}/V_{O_2}$ slope</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{O_2}$ peak (l min$^{-1}$)</td>
<td>13.4 ± 3.4</td>
<td>13.8 ± 3.4</td>
<td>13.2 ± 4.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{E}/V_{O_2}$ slope</td>
<td>12.3 ± 23.2</td>
<td>12.2 ± 23.9</td>
<td>16.1 ± 39.3</td>
<td>&lt;0.019</td>
</tr>
<tr>
<td>$V_{O_2}$ peak (ml kg$^{-1}$ min$^{-1}$)</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V_{E}/V_{O_2}$ slope</td>
<td>3.2 ± 6.3</td>
<td>3.2 ± 5.8</td>
<td>3.4 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$V_{O_2}$ peak (ml kg$^{-1}$ min$^{-1}$)</td>
<td>18.8 ± 66.5</td>
<td>18.5 ± 66.5</td>
<td>16.1 ± 39.3</td>
<td>&lt;0.019</td>
</tr>
<tr>
<td>$V_{E}/V_{O_2}$ slope</td>
<td>21.1 ± 13.6</td>
<td>21.1 ± 13.6</td>
<td>16.1 ± 39.3</td>
<td>&lt;0.019</td>
</tr>
</tbody>
</table>

BMI: body mass index; FEV$1$: forced expiratory ventilation in 1 s; M: Male; NS: Not statistically significant; ppo: postoperative predicted value; VC: vital capacity; $V_{E}/V_{CO_2}$ slope: the ratio between minute ventilation ($V_{E}$) and carbon dioxide output ($V_{CO_2}$) during exercise; $V_{O_2}$ peak: maximal oxygen uptake at peak of exercise.
The only independent mortality predictor, and all patients with
Thoracic Surgeons [2], ATS [5] and American College of
have been made in recent years to determine these
limit of surgical tolerance is difficult [1, 2]. Several attempts
patients with lung cancer, even if the assessment of the lower
respiratory functional tests and CPET), the
according to ERS—ATS [5] after preoperative study including
Chest Physicians [1].

In our 145 consecutive patients (considered operable
according to ERS—ATS [5] after preoperative study including
respiratory functional tests and CPET), the $V_{E}/V_{CO2}$ slope was the only independent postoperative mortality predictor and no deaths occurred when the $V_{E}/V_{CO2}$ slope was in the normal range; (b) $V_{O2}$ peak, as previously reported [1, 4], is a good predictor of severe postoperative occurrence of cardiopulmonary complication.

Surgical resection remains the treatment of choice in patients with lung cancer, even if the assessment of the lower limit of surgical tolerance is difficult [1, 2]. Several attempts have been made in recent years to determine these physiological limits by ERS [2, 5], European Society of Thoracic Surgeons [2], ATS [5] and American College of Chest Physicians [1].

In our 145 consecutive patients (considered operable according to ERS—ATS [5] after preoperative study including respiratory functional tests and CPET), the $V_{E}/V_{CO2}$ slope was the only independent mortality predictor, and all patients with normal $V_{E}/V_{CO2}$ slope survived. According to previously published data [3–6], $V_{O2}$ peak (ml kg$^{-1}$ min$^{-1}$) and $p_{pcFEV1}$ (%predicted) were significantly lower in patients with severe postoperative complications; but these variables showed a poor correlation with postoperative mortality. Moreover, the $V_{O2}$ peak was the best predictor of the occurrence of severe cardiopulmonary postoperative complications. The $V_{O2}$ peak was the first exercise testing variable recognised as prognostic in many clinical situations, from the preoperative evaluation [2–5] in thoracic and general surgery to CHF patients’ management [10]. More recently, $V_{E}/V_{CO2}$ slope was recognised as a marker of pulmonary hypertension in COPD [7] patients, and its measurement has peculiar clinical relevance in patients with pulmonary hypertension [8] and CHF [9, 10, 16]. In fact, the $V_{E}/V_{CO2}$ slope was repeatedly identified as a strong and independent prognostic survival index in 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 $V_{O2}$ peak [9, 16], which underscores the clinical importance of ventilatory efficiency.

Mathematically, the $V_{E}/V_{CO2}$ slope is determined by three factors [16, 17]: the amount of CO$_2$ produced ($V'$), the physiological dead space/tidal volume ratio ($V_d/V_T$) and the arterial CO$_2$ partial pressure ($P_aCO_2$). The increase of the ventilation for the same CO$_2$ production can be explained by: (a) increased $V_d/V_T$ and consequent wasted ventilation [16, 17], (b) early occurrence of lactic acidosis [17] and (c) abnormal chemoreflex and/or metaboreflex activity [18, 19]. Pulmonary hypertension is, moreover, described as a cause of hyperventilation not only in CHF patients but also in patients with idiopathic pulmonary hypertension [20]. More recently, the $V_{E}/V_{CO2}$ slope was found increased [21] after lung resection in COPD patients. In our opinion, the reduction of the vascular bed after lung resection can worsen pulmonary haemodynamics, especially in patients with pre-existing subclinical pulmonary hypertension, and could therefore elicit hyperventilation. For similar reasons, lung transplantation is preferred to lung volume reduction in COPD with associated pulmonary hypertension [5].

It seems to be possible that COPD non-survivor patients might have worse haemodynamics, with sub-clinical pulmonary hypertension. Lung resection could stress this situation, promoting acute cardiopulmonary failure that represents the main cause of death in our population. Nutritional depletion is associated with poor outcomes and increased risk of postoperative complications [22]. Although some studies [22] have confirmed that lung cancer patients who underwent surgery are often nutritionally depleted and predisposed to postoperative complications, in more recent studies [23], nutritional status does not seem to influence significantly the immediate outcomes after lobectomy for lung cancer. On the contrary, there is agreement that nutritional status affects long-term survival after lobectomy for lung cancer [24]. Our patients with poor outcome had a low BMI, but logistic regression rejected this parameter from the final regression, even if at the limit of statistical significance.

In our population, only the $V_{O2}$ peak, expressed as absolute value in litres per minute, was either significantly different between survivors or not. This finding suggests caution in analysing preoperative data that consider $V_{O2}$ peak expressed as ml kg$^{-1}$ min$^{-1}$ in patients with low BMI. The lower the weight, the higher is the $V_{O2}$ peak if expressed as ml kg$^{-1}$ min$^{-1}$, leading to a misleading interpretation of the cardiopulmonary performance.

The present study has some limitations. The data are retrospectively analysed on a set of patients considered operable according to criteria, previously validated, that did not consider ventilation inefficiency. On the other hand, although this population was relatively large, the absolute number of non-survivors was very low. The observation that $V_{E}/V_{CO2}$ slope can be considered as a postoperative mortality predictor should be tested in further larger series of patients with a prospective approach.

6. Conclusions

In COPD patients considered operable, after a preoperative study including a CPET that showed an acceptable cardiopulmonary performance, a high $V_{E}/V_{CO2}$ slope is an independent mortality predictor.

Considering that increase in the $V_{E}/V_{CO2}$ slope can be a marker of pulmonary hypertension, to optimise preoperative
evaluation, we suggest that COPD patients showing an increase in $V_{E}/V_{CO2}$ slope must be carefully screened to exclude pulmonary hypertension, especially before surgical procedures with large parenchymal excision.

References


[3] Arena R, Myers J, Abella J, Peberdy MA, Bensimhon O, Chase P, Guazzi M. Ventilatory expired gas techniques during cardiopulmonary exercise testing, we suggest that COPD patients showing an increase in $V_{E}/V_{CO2}$ slope must be carefully screened to exclude pulmonary hypertension, especially before surgical procedures with large parenchymal excision. Eur Respir J 2009;34:17—41.


Editorial comment

Beyond peak $V_{O2}$: ventilatory inefficiency ($V_{E}/V_{CO2}$ slope) measured during cardiopulmonary exercise test to refine risk stratification in lung resection candidates

Keywords: Pulmonary resection; Peak $V_{O2}$; Ventilatory inefficiency; Cardiopulmonary exercise tests; Risk stratification

Ventilatory expired gas techniques during cardiopulmonary exercise testing (CPET) have become more widely applied because they significantly increase the precision and yield of information from the exercise test [1]. The identification of peak $V_{O2}$ as an important independent predictor of severity of heart disease and also prognosis has been recently updated by the evidence that ventilation plays a role in improving predictive accuracy of CPET. Responses such as $V_{E}$, $V_{E}/V_{CO2}$ slope, $V_{E}/V_{CO2}$ at peak exercise, oscillatory ventilation, oxygen uptake kinetics, rate of recovery of $V_{O2}$ and oxygen uptake efficiency slope have been used with greater frequency to classify functional limitations and to stratify risk in patients with heart disease. Many of these are expressions of ventilatory efficiency and reflect the various