Impact of aerobic exercise capacity and procedure-related factors in lung cancer surgery

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Abstract

Over the past decades, major progress in patient selection, surgical techniques and anaesthetic management have largely contributed to improved outcome in lung cancer surgery. The purpose of this study was to identify predictors of post-operative cardiopulmonary morbidity in patients with a forced expiratory volume in 1 s 17 mL·kg⁻¹·min⁻¹, those with a peak V'(O₂)

Reference


DOI : 10.1183/09031936.00069910
PMID : 20847073
Impact of aerobic exercise capacity and procedure-related factors in lung cancer surgery


ABSTRACT: Over the past decades, major progress in patient selection, surgical techniques and anaesthetic management have largely contributed to improved outcome in lung cancer surgery. The purpose of this study was to identify predictors of post-operative cardiopulmonary morbidity in patients with a forced expiratory volume in 1 s <80% predicted, who underwent cardiopulmonary exercise testing (CPET).

In this observational study, 210 consecutive patients with lung cancer underwent CPET with completed data over a 9-yr period (2001–2009).

Cardiopulmonary complications occurred in 46 (22%) patients, including four (1.9%) deaths. On logistic regression analysis, peak oxygen uptake (peak VO₂) and anaesthesia duration were independent risk factors of both cardiovascular and pulmonary complications; age and the extent of lung resection were additional predictors of cardiovascular complications, whereas tidal volume during one-lung ventilation was a predictor of pulmonary complications. Compared with patients with peak VO₂ >17 mL kg⁻¹ min⁻¹, those with a peak VO₂ <10 mL kg⁻¹ min⁻¹ had a four-fold higher incidence of cardiac and pulmonary morbidity.

Our data support the use of pre-operative CPET and the application of an intra-operative protective ventilation strategy. Further studies should evaluate whether pre-operative physical training can improve post-operative outcome.

KEYWORDS: Cardiopulmonary exercise test, lung cancer, lung resection, peak oxygen consumption, post-operative morbidity

To date, lung resection is the only curative option for the early stages of lung cancer. Overall, perioperative mortality rates range between 2% and 5% and the incidence of post-operative cardiopulmonary complications varies between 20% and 40%, resulting in prolonged hospital stay and increased healthcare costs [1–3]. Although up to 25% of patients may benefit from surgical resection, in the remaining patients, either the cancer stage is considered too advanced or comorbidities are judged too severe, precluding any benefit in terms of post-operative survival and quality of life [4].

Basically, selection criteria for lung resection entail a stepwise approach with distinct targets, first determining the resectability of the tumour, then assessing the severity of comorbidities and finally questioning the expected functional capacity following lung resection [5–7]. Besides imaging techniques and lung functional investigations, cardiopulmonary exercise testing (CPET) has recently emerged as a noninvasive tool providing valuable diagnostic and prognostic information [8–10]. During incremental physical workload, the physiological reserve of the heart, lungs and skeletal muscles can be quantified by monitoring ECG changes, heart rate and blood pressure responses, respiratory volumes, oxygen consumption and carbon dioxide production, as well as by grading dyspnoea and subjective feelings. Accordingly, interpretation of abnormal results during CPET is helpful for detecting significant coronary artery disease, ventricular or valvular dysfunction, gas exchange or ventilation abnormalities as well as skeletal muscle deconditioning [8, 11].

Several prospective studies have demonstrated that limitation of exercise capacity as expressed by peak oxygen uptake (peak VO₂) or maximal oxygen uptake was strongly predictive of perioperative mortality and cardiopulmonary morbidity [12–15]. Based on these data, CPET has been endorsed by the European Respiratory Society

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Received: May 04 2010
Accepted after revision: Aug 30 2010
First published online: Sept 16 2010

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003
(ERS) and the European Society of Thoracic Surgery (ESTS) and incorporated in a functional algorithm for the evaluation of candidates for lung resection [16, 17]. These updated guidelines recommend that formal CPET should be performed in all surgical candidates with forced expiratory volume in 1 s (FEV1) or with diffusing capacity of the lung for carbon monoxide (DLCO) <80% of predicted values. Interestingly, this algorithm dates back to the mid-1990s, being tested and subsequently validated in two cohorts of 80 and 135 patients [18, 19]. Since this pioneering work, advances in surgical techniques and anaesthetic management have led to improved perioperative outcomes, despite increasing proportions of elderly and higher-risk patients [2, 20, 21].

In this study, we retrospectively analysed all lung resection candidates who underwent formal CPET according to the ERS/ESTS guidelines in our institution over the past decade. The main objective was to re-examine predictors of in-hospital cardiac and pulmonary morbidity based on patient comorbidity indices, various parameters of CPET and intra-operative procedure-related factors.

**MATERIAL AND METHODS**

**Study design and settings**

This was an observational cohort analysis performed on data prospectively collected in patients who underwent lung resection for lung cancer from January 2001 to December 2009 in a tertiary referral hospital (n = 243 patients). The study population included surgical candidates with FEV1 <80% pred who underwent CPET according to an algorithm initially proposed by Bolliger et al. [19] and updated in 2009 by a task force of the ERS/ESTS [16, 17]. The study and the database were approved by the local institutional review board and informed consent was waived, given the retrospective analysis of existing documents and the anonymised database. All patients were operated on by a board-certified thoracic surgeon and were managed by the same team of cardiothoracic anaesthetists and chest physicians.

**Patients and perioperative management**

Besides clinical evaluation, ECG and laboratory screening, routine pre-operative work-up included pulmonary function tests (SensorMedics; Yonba Linda, CA, USA), lung biopsy, computed tomography (CT) scan and/or positron emission tomography of the chest and abdomen. Patients with abnormal spirometric results (FEV1 <80% pred), impaired exercise tolerance or cardiac risk factors, underwent complementary investigations, including CPET and DLCO.

Symptom-limited CPET was performed on an upright electronically braked cycle ergometer (SensorMedics 2200 SP; SensorMedics). After a 2-min warm-up period at 20 W, an incremental protocol with 20 W-min⁻¹ workload increases was started. The exercise test was stopped when the patients were exhausted, or at any ECG signs or clinical symptoms of myocardial ischaemia, including a fall in systolic blood pressure. Peak VO₂ was expressed in mL·min⁻¹·kg⁻¹ body weight and in mL·min⁻¹·kg⁻¹ predicted body weight (PBW) [22].

Before surgical incision, antimicrobial prophylaxis was administered (cefuroxime 1.5 g as a single dose). Lung resection with systematic lymph node sampling was performed through an anterolateral muscle-sparing thoracotomy while the contralateral lung was selectively ventilated with tidal volume (VT) ranging from 4 to 10 mL·kg⁻¹ and with variable levels of positive end-expiratory pressure (PEEP; 0–10 cmH₂O). Fast-track anaesthetic modalities entailed the administration of short-acting anaesthetic agents and low doses of intravenous opiates, provision of continuous thoracic epidural analgesia, monitoring neuromuscular blockade and goal-directed intravenous fluid loading. All patients were extubated in the operating theatre and were managed over the next 12–24 h in the post-anaesthesia recovery room before being transferred to the thoracic surgical unit. Post-operative management was standardised with particular emphasis on early feeding with close control of fluid balance, active mobilisation with lung recruitment manoeuvres and provision of multimodal analgesia, including nonsteroidal anti-inflammatory drugs, paracetamol and thoracic epidural blockade. Parenteral morphine was only administered to patients with contraindication for epidural puncture or non-functioning/displaced epidural catheter (10 (4.1%) out of 243 patients).

**Data collection**

The primary composite morbidity rate included operative mortality (death within 30 days of surgery or later if the patient was still hospitalised), as well as cardiovascular complications (myocardial infarction, arrhythmias, congestive heart failure, stroke, thromboembolism or renal dysfunction) and pulmonary complications (atelectasis, pneumonia or acute lung injury (ALI)) as detailed in the appendix and consistent with previous studies [2, 13].

Demographic, clinical, surgical and anaesthetic data, as well as pathological stage and perioperative complications, were recorded on a case report form for the index hospitalisation. Respiratory functional data included ergometric parameters (peak VO₂, workload, maximal ventilatory capacity and arterial oxygen pressure), baseline spirometric values and the predicted post-operative FEV1 (ppo FEV1) calculated by taking into account the number of open and functional segments removed [5].

Intra-operatively, the following items were also recorded: VT during one-lung ventilation, amount of vasopressor drugs, urine output and fluid intake (colloids, crystalloids and blood products). All these data (94 items) were entered into a surgical database and cross-checked for accuracy.

**Statistical analysis**

Perioperative clinical, surgical and ergonomic characteristics of patients with and without cardiovascular or respiratory complications (or both) were compared with the Chi-squared test for categorical variables (expressed in percentage) and the unpaired t-test (normal distribution) or Wilcoxon rank test (non-Gaussian distribution) for continuous variables (all expressed as mean ± SD).

Variables that had a univariate probability value <0.20 or those judged to be clinically important were selected for inclusion in a logistic regression model. To avoid multicollinearity, only one variable was retained in a set of variables with the highest correlation coefficient (>0.5). Independent predictors of cardiovascular and/or respiratory morbidity and factor-adjusted odds ratios with 95% confidence intervals were calculated. To further assess the reliability of the predictors,
regression was repeated in 1,000 random bootstrap samples from the original dataset. Given the small number of perioperative deaths (only four cases), mortality was not separately analysed and these cases were included in morbidity analysis according to the type of complications. Model discrimination was evaluated by the area under the receiver operating characteristic (ROC) curve, and calibration was assessed with the Hosmer–Lemeshow goodness-of-fit statistic. All analysis were performed using SPSS software version 14.0 (SPSS, Chicago, IL, USA) and Stata software version 11.0 (Stata Corp, College Station, TX, USA). Statistical significance was specified to a two-tailed type I error (p-value) set below the 0.05 level.

RESULTS
A total of 210 patients with FEV1 <80% pred yielded completed datasets and were included in the study (fig. 1). Table 1 shows the baseline characteristics of patients stratified by peak V'O2. Patients with low peak V'O2 (<17 mL·kg⁻¹·min⁻¹) were more likely to be older, female and hypertensive; they also presented with a higher body mass index (BMI), higher American Society Association (ASA) risk classes, lower FEV1 (pre-operative and predicted post-operative values) and with earlier pathological stages. Rates of coronary artery disease, hypercholesterolaemia, diabetes mellitus, as well as smoking and alcohol status, did not differ significantly among the stratified peak V'O2 groups.

Peak V'O2 expressed in mL·min⁻¹·kg⁻¹ PBW was higher than peak V'O2 expressed in mL·min⁻¹·kg⁻¹ absolute body weight (18.50 ± 5.7 versus 16.0 ± 5.3; p=0.0003).

As described in table 2, 30-day mortality was 1.9% and all four deaths occurred in patients with peak V'O2 <17 mL·kg⁻¹ and were primarily related to cardiovascular complications (n=3) and ALI (n=1). 46 patients experienced at least one cardiopulmonary complication (incidence of 22%). 36 pulmonary complications occurred in 28 patients (pneumonia, 18 cases; atelectasis, 15 cases; ALI, three cases). 30 cardiovascular complications occurred in 24 patients (arrhythmias, 17 cases; stroke, three cases; acute heart failure, six cases; myocardial infarction, two cases; pulmonary embolism, two cases). 16 patients presented with both cardiovascular and pulmonary complications. Overall, the incidence of complications did not differ in patients undergoing minor or major lung resection (19.2% versus 20.5%, respectively; p=0.701).

In univariate analysis, patients experiencing cardiopulmonary complications had lower pre-operative V'O2, they underwent longer and more extensive procedures and required larger doses of vasopressors at the time of surgery; in addition, a higher BMI was associated with a higher incidence of respiratory complications (table 3). In contrast, sex, smoking habits, alcohol consumption, the presence of coronary artery disease, hyperlipidaemia or diabetes mellitus did not differ between groups of patients with or without complications. After adjusting for other perioperative factors by logistic regression, peak V'O2 and anaesthesia duration remained independent predictors of cardiovascular and/or pulmonary complications; age and the extent of lung resection (pneumonectomy or bilobectomy) were additional predictors of cardiovascular complications whereas VT during one-lung ventilation was an independent risk factor of respiratory complications (table 4).
As detailed in Table 5, ROC curve analysis showed that the best cut-off values for peak VO₂ to predict cardiac complications were 13.6 mL·min⁻¹·kg⁻¹ and 16.2 mL·min⁻¹·PBW⁻¹ (c-indices, 0.71 versus 0.74, respectively; p=0.445) whereas for pulmonary complications the best cut-off values were 12.8 mL·min⁻¹·kg⁻¹ and 15.8 mL·min⁻¹·PBW⁻¹ (c-indices, 0.72 versus 0.65, respectively; p=0.304).

The incidence of cardiovascular and pulmonary complications increased in parallel with the reduction in peak VO₂ during exercise testing (Fig. 2). Compared with patients with peak VO₂ >17 mL·kg⁻¹·min⁻¹, those with a peak VO₂ <10 mL·kg⁻¹·min⁻¹ had a four-fold higher incidence of cardiac and pulmonary morbidity.

**DISCUSSION**

In this retrospective analysis of surgical candidates with FEV₁ <80%, we demonstrated that markers of pre-operative cardiopulmonary fitness and the duration of anaesthesia were the best predictors of cardiopulmonary complications following lung cancer surgery. In addition, age and the extent of lung resection were also considered independent risk factors of cardiovascular complications, whereas VT during one-lung ventilation was a predictor of pulmonary complications.

Among CPET parameters, peak VO₂ values had the best discriminative power to identify the high-risk group of patients. In agreement with previous reports, we confirmed that a peak VO₂ >20 mL·kg⁻¹·min⁻¹ is a safe cut-off value for lung resection since no mortality and <8% respiratory and cardiac complications occurred above this threshold [13, 23, 24, 25]. In contrast, below 10 mL·kg⁻¹·min⁻¹ peak VO₂ patients experienced a four-fold higher incidence of cardiovascular and pulmonary complications, compared with surgical candidates presenting peak VO₂ values >20 mL·kg⁻¹·min⁻¹. Nevertheless, the use of peak VO₂ expressed in mL·kg⁻¹ may lead to exclusion of obese candidates who are actually fit enough to undergo surgery. As peak VO₂,max better correlates with lean body mass than total
Given the prognostic importance of ppo FEV1 regarding providing minimal loss or even improvement in lung function in patients with chronic obstructive pulmonary disease (COPD), a result of inadequate pain control, residual effects of anaesthesia, fluid overload, ventilator-induced lung injuries, increased surgical stress-induced metabolic demand by linking a low aerobic capacity with a high-risk profile, one might have achieved by using perfusion scintigraphy, quantitative CT or magnetic resonance imaging [29].

Although there is no firmly identified causal mechanism of low aerobic capacity with a high-risk profile, one explanation is that “unfit” patients are unable to face the increased surgical stress-induced metabolic demand by linking a low aerobic capacity with a high-risk profile [11]. Pre-existing disturbances in cardiac pumping performances, respiratory function and oxygen utilisation within the skeletal muscles may worsen during the early post-operative period as a result of inadequate pain control, residual effects of anaesthesia, fluid overload, ventilator-induced lung injuries, direct surgical nerve damage, reflex inhibition of diaphragmatic function and muscular fatigue associated with systemic...
inflammation and enhanced protein catabolism. Indeed, patients with the lowest peak $V'\text{O}_2$ values ($<17 \text{ mL-kg}^{-1}\text{-min}^{-1}$) presented a higher index of comorbidity as reflected by ASA risk classes, a higher prevalence of arterial hypertensive disease and greater impairments in pulmonary function. Finally, oxidative stress has been shown to accelerate protein breakdown and to trigger nuclear apoptosis in unloaded skeletal muscle, thereby rendering these patients unable to sustain an adequate ventilatory response [30].

Previous investigators have limited their analysis mainly to preoperative clinical and functional parameters that could affect the early post-operative outcome [13–15, 19, 25, 31]. In the present study, we assessed >90 potential risk factors focusing on patient pre-operative condition but also on intra-operative markers of processes of care. In this regard, prolonged anaesthetic time probably reflected the dual aspects of a complex surgical approach as well as difficulties with anaesthesia emergence and weaning from the ventilator. Extended tissue dissection involving ischaemia-reperfusion injuries would obviously impose larger post-operative metabolic needs and greater loads on the cardiovascular and respiratory systems.

Not surprisingly, we found that age and performing a pneumonectomy or bilobectomy were additional risk factors for the occurrence of cardiac complications. Indeed, excess collagen deposition in the extracellular matrix coupled with a progressive loss of cardiac myocytes by apoptotic cell death are hallmarks of the senescent heart that have been incriminated in the pathogenesis of ventricular dysfunction and atrial fibrillation [32]. Moreover, the pulmonary circulatory system becomes less compliant after extended parenchymal lung resection, resulting in increased right ventricular afterload [33]. However, autonomic nerve injuries occur inevitably when surgical dissection involves the hilar mediastinal structures [34]. Accordingly, the majority of cardiovascular complications consisting of arrhythmias (8%) and acute heart failure (3%) were probably related to age-associated myocardial remodelling, cardiac autonomic nerve imbalance and greater vulnerability to fluid loading.

Besides markers of cardiopulmonary fitness and the duration of anaesthesia, we found that the intra-operative ventilatory strategy significantly influenced the development of pneumonectomy or bilobectomy with large volumes of postoperative ventilation being associated with higher operative risk. Consistent with this finding, $V_t >7-8 \text{ mL-kg}^{-1}$ or elevated inspiratory pressure during one-lung ventilation have been associated with greater risks to develop ALI and with larger release of cytokines within the lungs and the systemic circulation [35, 36]. Conversely, the application of "physiological" $V_t$ (4–7 mL-kg$^{-1}$) and external PEEP in patients with healthy lungs undergoing oesophagectomy has been associated with an attenuated systemic pro-inflammatory response, lower interstitial pulmonary oedema and a better oxygenation index [37]. Performing vital capacity manoeuvres has also been known to re-expand the collapsed dependent lung areas that develop in almost all anaesthetised patients, whereas moderate levels of PEEP are known to prevent a subsequent fall in functional residual capacity by preventing cyclic opening–closing within pulmonary alveoli and peripheral airways [21, 38]. Given the strong body of scientific knowledge related to perioperative ventilator-associated injuries, we have adopted a lung-protective protocol involving small $V_t$, external

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**TABLE 3**

Characteristics of the four patients who died within the perioperative period

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age yrs</th>
<th>Sex</th>
<th>BMI kg m$^{-2}$</th>
<th>Operation</th>
<th>Comorbidities</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>M</td>
<td>28.7</td>
<td>RUL</td>
<td>Alcohol$^*$</td>
<td>Stroke (day 6)</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>26.3</td>
<td>LP</td>
<td>CAD, Hyperlipidaemia, Alcohol$^*$</td>
<td>Myocardial infarction, stent thrombosis, heart failure (day 10)</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>27.9</td>
<td>RP</td>
<td>Hypertension</td>
<td>ALI, MOF (day 9)</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>27.2</td>
<td>LUL</td>
<td>Hypertension, Hyperlipidaemia</td>
<td>Pulmonary thromboembolism (day 4)</td>
</tr>
</tbody>
</table>

BMI: body mass index; M: male; F: female; $V'$O$_2$: oxygen uptake, ppo: predicted post-operative, $V't$: tidal inspiratory volume in 1 s, RUL: right upper lobectomy, LP: left pneumonectomy, CAD: coronary artery disease; ALI: acute lung injury, MOF: multiple organ failure; LUL: left upper lobectomy. $^*$: expressed in mL min$^{-1}$ kg$^{-1}$ absolute body weight; $^\#: 21$ drinks per week for men or $14$ drinks per week for women.

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PEEP and periodical recruitment manoeuvres since March 2003. Over the following 5-yr period, implementation of this “open-lung” strategy was associated with a reduced incidence of ALI and atelectasis, along with fewer admissions in intensive care [39].

There are some limitations and strengths of this observational study that should be mentioned. First, although 90 items were prospectively collected, we assume some variability in recorded data, unmeasured risk factors and diseases with low prevalence rate (e.g. diabetes mellitus and pulmonary hypertension) that could partly confound the interpretation of the multivariate analysis. Secondly, we obtained peak VO₂ data using bicycle exercise that might not be feasible in patients with lower extremities disabilities caused by vascular, neurological

| TABLE 4 | Results of logistic regression analysis for different dependent variables |
|----------------|-----------------|-----------------|-----------------|---------------|---------------|
| **Independent predictor** | **Coefficient** | **SEM** | **OR (95% CI)** | **p-value** | **Bootstrap frequency %** |
| **Total morbidity** | | | | | |
| Constant | 0.2980 | | | | 79 |
| Duration of anaesthesia | 0.0145 | 0.0041 | 1.015 (1.006-1.023) | 0.0005 | |
| Peak VO₂ in mL·min⁻¹·kg⁻¹ | -0.2353 | 0.0546 | 0.79 (0.71-0.88) | <0.0001 | 81 |
| **Cardiovascular complications** | | | | | |
| Constant | -6.5727 | | | | 62 |
| Age | 0.0804 | 0.0318 | 1.084 (1.018-1.153) | 0.0115 | |
| Duration of anaesthesia | 0.0143 | 0.0045 | 1.014 (1.005-1.024) | 0.0016 | 72 |
| Pneumonectomy or bilobectomy | 1.7518 | 0.5674 | 5.76 (1.90-17.53) | 0.0020 | 71 |
| Peak VO₂ mL·min⁻¹·kg⁻¹ | -0.2286 | 0.0768 | 0.80 (0.68-0.92) | 0.0029 | 69 |
| **Pulmonary complications** | | | | | |
| Constant | -21.0904 | | | | 66 |
| Duration of anaesthesia | 0.0133 | 0.0042 | 1.013 (1.006-1.022) | 0.032 | |
| Peak VO₂ mL·min⁻¹·kg⁻¹ | -0.1752 | 0.0590 | 0.840 (0.749-0.942) | 0.021 | 70 |
| V̇t mL·kg⁻¹ PBW | 2.8249 | 0.5384 | 1.65 (1.27-4.49) | 0.003 | 77 |

VO₂: oxygen uptake; V̇t: tidal volume; PBW: predicted body weight.

| TABLE 5 | Areas under the receiver operating characteristic curves and cut-off values of various parameters for the prediction of cardiovascular and pulmonary complications |
|----------------|-----------------|-----------------|-----------------|---------------|---------------|
| **Area under the curve** | **SE** | **Lower–upper bound** | **p-value** | **Cut-off** | **Sensitivity %** | **Specificity %** |
| **Total morbidity** | | | | | | |
| VO₂ kg⁻¹ | 0.717 | 0.045 | 0.651-0.777 | 0.0001 | 12.8 | 51 | 85 |
| VO₂ kg⁻¹ PBW | 0.710 | 0.045 | 0.643-0.771 | 0.0001 | 15.8 | 64 | 69 |
| VO₂ % pred | 0.657 | 0.045 | 0.589-0.722 | 0.0010 | 58 | 75 | 48 |
| ASA score | 0.593 | 0.039 | 0.523-0.661 | 0.0156 | 3 | 71 | 48 |
| ppo FEV₁ | 0.565 | 0.045 | 0.495-0.633 | 0.7880 | 64 | 65 | 49 |
| **Cardiovascular complications** | | | | | | |
| VO₂ kg⁻¹ | 0.708 | 0.065 | 0.640-0.771 | 0.0011 | 13.6 | 63 | 72 |
| VO₂ kg⁻¹ PBW | 0.738 | 0.054 | 0.671-0.798 | 0.0001 | 16.2 | 75 | 61 |
| VO₂ % pred | 0.633 | 0.061 | 0.562-0.700 | 0.0029 | 53 | 64 | 61 |
| ASA score | 0.630 | 0.046 | 0.560-0.695 | 0.0080 | 3 | 79 | 47 |
| ppo FEV₁ % pred | 0.492 | 0.066 | 0.422-0.562 | 0.9030 | 80 | 29 | 79 |
| **Pulmonary complications** | | | | | | |
| VO₂ kg⁻¹ | 0.723 | 0.057 | 0.654-0.784 | 0.0001 | 12.3 | 56 | 86 |
| VO₂ kg⁻¹ PBW | 0.691 | 0.065 | 0.580-0.718 | 0.0020 | 12.1 | 45 | 94 |
| VO₂ % pred | 0.616 | 0.066 | 0.544-0.684 | 0.0169 | 37 | 30 | 95 |
| ASA score | 0.597 | 0.044 | 0.527-0.664 | 0.0269 | 3 | 73 | 47 |
| ppo FEV₁ | 0.545 | 0.051 | 0.480-0.614 | 0.3716 | 64 | 73 | 50 |

VO₂: oxygen uptake; PBW: predicted body weight; % pred: % predicted; ASA: American Society Association; FEV₁: forced expiratory volume in 1 s; ppo: predicted post-operative.
or orthopedic conditions. In such cases, arm exercise testing should be considered as a suitable alternative [40]. Thirdly, our findings obtained in a referral thoracic centre cannot be generalised to nonspecialised units in the absence of standardised clinical pathways. Implementation of bundles of scientifically-based interventions has been shown to improve perioperative outcome. If we compare the current data with those published previously [26], we have witnessed a 25% reduction in cardiopulmonary morbidity over the past 15 yrs; this is probably attributable to the beneficial effects of thoracic epidural analgesia, fluid titration guided by Doppler flow monitoring and protective lung ventilation [2, 39, 41].

Our selection criteria were less restrictive than in the initial algorithm since 29 patients with peak \( V'O_2 <10 \text{ mL\cdotkg}^{-1}\cdot\text{min}^{-1} \) were considered suitable candidates for surgery, with 25 survivors, 14 of whom were without any serious complications. The majority of these very high-risk patients presented with early cancer stages IA and IB (55%) and moderate-to-severe COPD. Although no firm conclusions could be drawn from these encouraging data, some patients deemed inoperable (or at very high-risk) according to their very low peak \( V'O_2 \) values might become eligible for curative surgery, particularly those with acceptable ppo FEV1/ppo DL,CO values (≤80%). Given substantial progress in surgical techniques and anaesthetic management over the last decades, even high-risk patients (peak \( V'O_2 <10 \text{ mL\cdotkg}^{-1}\cdot\text{min}^{-1} \)) may be considered for life-saving surgery. According to our results, several risk-reducing strategies can be implemented: 1) patient referral to a qualified and experienced thoracic team in order to shorten the time of intervention; 2) application of a protective ventilatory protocol to minimise pulmonary injuries triggered by mechanical ventilation; and 3) considering short-term pre-operative physical training in the “unfit” patients. Further studies are needed to replicate our observations and to question whether improved aerobic capacity achieved by exercise training is associated with better post-operative outcome in the high-risk group.

**APPENDIX: MAJOR OUTCOMES**

**Mortality**

Death within 30 days after surgery or for a longer period if the patient was still hospitalised.

**Cardiovascular**

1) Myocardial infarction: typical rise and fall of creatine phosphokinase (CPK) (>120 U-L\(^{-1}\)) and MB isoform of creatine kinase/CPK >6% or troponin-I >1.5 ng-mL\(^{-1}\) with at least one of the following criteria: ischaemic symptoms, development of pathological Q waves on the ECG, ST segment elevation or depression (≥1 mm) or coronary artery intervention.

2) Arrhythmias: supraventricular and ventricular tachyarrhythmias on ECG causing unstable haemodynamic condition and requiring anti-arrhythmic medications and/or electrical cardioversion.

3) Congestive heart failure: need for sympathomimetic support, diuretics or vasodilators consistent with clinical, haemodynamic (pulmonary artery pressure ≥15 mmHg) and radiological evidence of pulmonary congestion.

4) Thrombo-embolism: acute occlusion of pulmonary arteries diagnosed by scintigraphy or angiogram.

5) Stroke: focal neurological deficit (transient or permanent).

6) Renal dysfunction: elevation of serum creatinine >50% compared with pre-operative value.

**Respiratory**

1) Atelectasis: lobar collapse (chest radiograph), need for continuous positive airway pressure and/or bronchoscopy.

2) Bronchopneumonia: temperature >38 °C, hyperleukocytosis (neutrophils), new lung infiltration (chest radiograph), positive culture (bronchial secretions or alveolar fluid).

3) Acute lung injury: 1) sudden onset of respiratory distress; 2) infiltrates on the chest radiograph consistent with pulmonary oedema; 3) impaired oxygenation with an arterial oxygen saturation of <90%.

The beneficial physiological effects of a short-term supervised training programme, namely an increase in peak \( V'O_2 \) (+20%) and in anaerobic threshold (10%), a reduction in plasma inflammatory markers and improvement in cardiac function [44–47].

In conclusion, our data strongly support the use of CPET for risk stratification in patients with pre-operative FEV1 <80%. Given substantial progress in surgical techniques and anaesthetic management over the last decades, even high-risk patients (peak \( V'O_2 <10 \text{ mL\cdotkg}^{-1}\cdot\text{min}^{-1} \)) may be considered for life-saving surgery. According to our results, several risk-reducing strategies can be implemented: 1) patient referral to a qualified and experienced thoracic team in order to shorten the time of intervention; 2) application of a protective ventilatory protocol to minimise pulmonary injuries triggered by mechanical ventilation; and 3) considering short-term pre-operative physical training in the “unfit” patients. Further studies are needed to replicate our observations and to question whether improved aerobic capacity achieved by exercise training is associated with better post-operative outcome in the high-risk group.
pressure-to-inspired oxygen fraction ratio <300 mmHg; and 4) absence of cardiac insufficiency or fluid overload, based on pulmonary arterial catheterisation, echocardiogram and/or clinical evaluation.

STATEMENT OF INTEREST
None declared.

REFERENCES


