Outcome after video-assisted thoracoscopic surgery and open pulmonary lobectomy in patients with low VO₂ max: a case-matched analysis from the ESTS database

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Abstract

OBJECTIVES: The aim was to verify the association of low VO₂ max with postoperative morbidity and mortality after video-assisted thoracoscopic surgery (VATS) or open pulmonary lobectomy using the European Society of Thoracic Surgeons (ESTS) database.

METHODS: A retrospective analysis of data collected from the ESTS database was conducted. A total of 1684 lobectomy patients with available VO₂ max values were included (2007–14). Patients operated through VATS (281 patients) or thoracotomy (1403 patients) were separately analysed. Propensity score analyses were performed to match patients with high (≥15 ml/kg/min) and low VO₂ max (<15 ml/kg/min) for each approach. The following variables were used to construct the score: age, body mass index, predicted postoperative forced expiratory volume in 1 s (%), coronary artery disease, American Society of Anaesthesiology grade and Eastern Cooperative Oncology Group performance score. Cardiopulmonary morbidity and 30-day mortality were compared between the matched groups.

RESULTS: Mean VO₂ max was 17.4 ml/kg/min. A total of 471 patients (28%) had low VO₂ max. Overall postoperative cardiopulmonary morbidity and mortality rates were 30% (505 patients) and 4.1% (70 patients), respectively. Morbidity and mortality rates in low VO₂ max patients were 33% (156 patients) and 6% (28 patients), respectively. After VATS, cardiopulmonary morbidity and mortality rates were 2-fold (13 of 72, 18% vs 143 of 399, 36%, P = 0.003) and 5-fold (1 of 72, 1.4% vs 27 of 399, 6.7%, P = 0.09) lower compared with thoracotomy. Matched comparison after thoracotomy (399 pairs): Mortality was significantly higher in patients with low VO₂ max (27 patients, 6.7%) compared with those with high VO₂ max (11 patients, 2.8%, P = 0.008). Complication rates were similar between the two groups (low VO₂ max: 143 patients, 36% vs high VO₂ max: 133 patients, 33%, respectively, P = 0.5). Matched comparison after vats (72 pairs): Morbidity and mortality rates of patients with low VO₂ max were similar to those of patients with high VO₂ max (morbidity: 13 patients, 18% vs 17 patients, 24%, P = 0.4; mortality: 1 patient, 1.4% vs 4 patients, 5.5%, P = 0.4).

CONCLUSIONS: Low VO₂ max was not associated with an increased surgical risk after VAT lobectomy, which challenges the traditional operability criteria when this technique is used.

Keywords: VAT lobectomy • Morbidity • Mortality • VO₂ max

INTRODUCTION

Cardiopulmonary exercise testing (CPET) is increasingly used to assess the aerobic capacity of the lung resection candidates. Several studies have shown that a VO₂ max lower than 10–15 ml/kg/min increases the postoperative risk of morbidity and mortality.

On the basis of this evidence, CPET has become one of the pivotal parameters to define the surgical risk in functional guidelines [6, 7]. However, current guidelines are based on the evidence derived from studies including patients operated on mainly through a thoracotomy approach. With the advent of video-assisted thoracoscopic surgery (VATS), an increasing number of procedures are now being performed via this approach.

[1–5]
Several studies have shown that VAT lobectomy is associated with reduced morbidity and mortality rates compared with open lobectomies [8–10]. The benefits of VATS are particularly evident in patients with prohibitive pulmonary function [11–14].

However, to date, there is a paucity of data assessing the outcome of VAT lobectomy patients with impaired VO2 max. It seems plausible that the use of VATS will challenge the operability cutoff values of VO2 max currently used for selecting patients for anatomical lung resection.

Therefore, the objective of this investigation was to query the European Society of Thoracic Surgeons (ESTS) database and verify the association between morbidity and mortality following VATS or open pulmonary lobectomy in patients with low VO2 max.

PATIENTS AND METHODS

The study protocol was submitted to the ESTS Database Committee for approval and release of an anonymized user file containing anatomical lung excision performed in patients with a preoperative VO2 max available.

Data source

The ESTS database is an online voluntary database launched in July 2007. It is free to all ESTS members and collects all general thoracic surgical procedures.

At the time of data extraction for this analysis, there were 235 participating sites within Europe (departments or individual surgeons). Variable definitions within the dataset are standardized and data entry consistency is ensured by the use of dropdown menu. Although there is no systematic data audit yet, a sample of data of several units participating to the ESTS accreditation programme has been audited to verify the accuracy of data collection [15]. The database characteristics, collection and maintenance have been previously described in detail [16, 17].

Patient population

The study population consists of patients submitted to VATS or open lobectomy for primary lung cancer and with a preoperative VO2 max available as a data element in the database, between 1 January 2007 and 31 December 2014. All data were collected using the online ESTS database.

Patients undergoing sublobar resections or pneumonectomies, redo operations and extended resection were not in the analysis.

A total of 31 124 lobectomies were present in the database at the time of the analysis. Of these, 1684 (5.4%) had preoperative VO2 max recorded in the database and constituted the final sample for the analysis and 1403 were operated through a thoracotomy and 281 through a VATS approach.

Definition of complications

Risk factors and outcomes were defined and standardized at database outset. Definitions can be found in the recently published paper by a collaborative task force of the STS and ESTS [18]. The following complications occurring in hospital or within 30 days from operation were included in the major cardiopulmonary morbidity outcome: adult respiratory distress syndrome, pneumonia, pulmonary embolism, pulmonary oedema, atelectasis requiring bronchoscopy, respiratory failure, arrhythmia requiring electrical or medical cardioversion, myocardial ischaemia, cardiac failure, stroke and acute renal failure.

Statistical analysis

We compared patients who underwent lobectomy via a VATS (281) approach with patients who underwent surgery via a thoracotomy (1403). To minimize selection bias, propensity score analyses were used to match patients with high (≥15 ml/kg/min) and low VO2 max (<15 ml/kg/min) for each approach [19, 20].

The following variables were used to construct the score: age, body mass index (BMI), predicted postoperative forced expiratory volume in 1 s (ppoFEV1%), coronary artery disease, American Society of Anaesthesiology (ASA) grade and Eastern Cooperative Oncology Group (ECOG) performance score. Predicted post operative Diffusing Capacity of the Lung for Carbon Monoxide (PpoDLCO) was not used for constructing the score as it was available in less than 50% of patients. The two matched groups were then compared in terms of cardiopulmonary morbidity and 30-day mortality using χ² or Fisher’s exact tests (in case of one or more of the cells have an expected frequency of 5 or less). Standardized differences (effect size) were used to assess the magnitude in differences of preoperative variables between the two groups. Effect size or standardized difference is calculated by dividing the difference in the averages of the two groups by the standard deviation in the total population. According to Cohen classification, an effect size between −0.2 and 0.2 indicates a small difference [21]. Standardized difference appears more appropriate than P-value to establish whether an adequate balance was achieved in matching, as it is less sensitive to sample size [22]. All tests were performed using the Stata 12 statistical software (Stata Corp., College Station, TX, USA).

RESULTS

Mean VO2 max in the entire population was 17.4 ml/kg/min. Four hundred and seventy-one patients (28%) had a low VO2 max. Figure 1 shows the distribution of VO2 max in the entire population of the ESTS database. Twenty-nine percent had a VO2 max greater than 20 ml/kg/min, whereas 28% had a VO2 max lower than 15 ml/kg/min. Overall postoperative cardiopulmonary
morbidity and mortality rates were 30% (505 patients) and 4.1% (70 patients), respectively.

**VO₂ max ≥15 ml/kg/min**

In this group of 1213 patients, postoperative cardiopulmonary and mortality rates were 29% (349 patients) and 3.5% (42 patients), respectively. Cardiopulmonary morbidity was lower in VATS patients compared with thoracotomy (47 of 209, 22% vs 302 of 1004, 30%, respectively. Cardiopulmonary morbidity was lower in VATS patients compared with thoracotomy (47 of 209, 5.2% vs thoracotomy 31 of 1004, 3%, $\chi^2$ test, $P = 0.03$). Mortality was similar in the two groups (VATS 11 of 209, 5.2% vs thoracotomy 31 of 1004, 3%, $\chi^2$ test, $P = 0.1$).

**VO₂ max <15 ml/kg/min**

In this group of 471 patients, postoperative cardiopulmonary and mortality rates were 33% (156 patients) and 6% (28 patients), respectively. Cardiopulmonary morbidity was lower in VATS patients compared with thoracotomy (47 of 1268 patients, 3.7% vs 302 of 1004, 3%, $\chi^2$ test, $P = 0.003$). Mortality was lower after VATS (VATS 1 of 72, 1.4% vs thoracotomy 27 of 399, 6.7%, Fisher's exact test, $P = 0.09$).

**Matched comparison after thoracotomy**

Mortality was significantly higher in patients with low VO₂ max (45 of 591 patients, 7.6%) compared with those with high VO₂ max (47 of 1268 patients, 3.7%, $\chi^2$ test, $P < 0.001$). Complication rates were also higher in patients with low VO₂ max (209 of 591 patients, 35% vs 388 of 1268 patients, 31%, respectively, $\chi^2$ test, $P = 0.04$).

**Matched comparison after thoracotomy (399 pairs)**

The characteristics of the patients in the two matched groups are presented in Table 1. Mortality was significantly higher in patients with low VO₂ max (27 patients, 6.7%) compared with those with high VO₂ max (11 patients, 2.8%, $\chi^2$ test, $P = 0.008$). Complication rates were similar between the two groups (143 patients, 36% vs 133 patients, 33%, respectively, $\chi^2$ test, $P = 0.5$). Propensity score-weighted logistic regression showed that low VO₂ max was significantly associated with mortality ($P = 0.002$) but not with complications ($P = 0.8$).

**Unmatched comparison after video-assisted thoracoscopic surgery**

Morbidity and mortality rates of patients with low VO₂ max were similar to those of patients with high VO₂ max (morbidity: 13 of 81 patients, 16% vs 57 of 242 patients, 24%, $\chi^2$ test, $P = 0.2$; mortality: 2 of 81 patient, 2.5% vs 13 of 242 patients, 5%, Fisher's exact test, $P = 0.4$).

**Matched comparison after video-assisted thoracoscopic surgery (72 pairs)**

The characteristics of the patients in the two matched groups are presented in Table 2. Morbidity and mortality rates of patients with low VO₂ max were similar to those of patients with high VO₂ max (morbidity: 13 patients, 18% vs 17 patients, 24%, $\chi^2$ test, $P = 0.4$; mortality: 1 patient, 1.4% vs 4 patients, 5.5%, Fisher's exact test, $P = 0.4$). Propensity score-weighted logistic regression showed that low VO₂ max was not significantly associated with mortality ($P = 0.2$) or with complications ($P = 0.09$).

**DISCUSSION**

CPET is being increasingly utilized in clinical practice to determine patients’ fitness for surgery. Initial studies suggested that CPET was a valuable test in assessing fitness for resection [2, 4]. Consequently, it has been incorporated into both the ESTS and

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**Table 1:** Characteristics of the patients submitted to open lobectomy in the two matched groups with VO₂ max above or below 15 ml/kg/min (399 pairs)

<table>
<thead>
<tr>
<th>Variables</th>
<th>VO₂ max &lt;15 ml/kg/min</th>
<th>VO₂ max ≥15 ml/kg/min</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.1 (9.5)</td>
<td>67.4 (8.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (5.1)</td>
<td>26.7 (5)</td>
<td>0.1</td>
</tr>
<tr>
<td>ppoFEV₁%</td>
<td>56.9 (15)</td>
<td>57.1 (14.6)</td>
<td>–0.01</td>
</tr>
<tr>
<td>ASA</td>
<td>2.5 (0.6)</td>
<td>2.4 (0.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>ECOG</td>
<td>0.97 (0.7)</td>
<td>0.92 (0.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>18</td>
<td>18</td>
<td>0.01</td>
</tr>
<tr>
<td>VO₂ max (ml/kg/min)</td>
<td>12.6 (1.7)</td>
<td>18.2 (2.9)</td>
<td>–1.6</td>
</tr>
</tbody>
</table>

Results are expressed as mean and standard deviations unless otherwise specified. Effect size or standardized difference is calculated by dividing the difference of the averages of the two groups by the standard deviation in the total population. Effect size: 0.2 = small difference; 0.5 = medium difference; 0.8 = large difference. BMI: body mass index; ppoFEV₁: predicted postoperative forced expiratory volume in 1 s; ASA: American Society of Anaesthesiology score; ECOG: Eastern Cooperative Oncology Group performance score; CAD: coronary artery disease.

**Table 2:** Characteristics of the patients submitted to VAT lobectomy in the two matched groups with VO₂ max above or below 15 ml/kg/min (72 pairs)

<table>
<thead>
<tr>
<th>Variables</th>
<th>VO₂ max &lt;15 ml/kg/min</th>
<th>VO₂ max ≥15 ml/kg/min</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.0 (7.8)</td>
<td>69.5 (8.1)</td>
<td>–0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 (5.1)</td>
<td>25.8 (5.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>ppoFEV₁%</td>
<td>58.6 (16.9)</td>
<td>60.8 (17.6)</td>
<td>–0.1</td>
</tr>
<tr>
<td>ASA</td>
<td>2.3 (0.7)</td>
<td>2.2 (0.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>ECOG</td>
<td>0.73 (0.6)</td>
<td>0.7 (0.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>19%</td>
<td>17%</td>
<td>0.06</td>
</tr>
<tr>
<td>VO₂ max (ml/kg/min)</td>
<td>12.5 (1.6)</td>
<td>18.2 (2.8)</td>
<td>–1.5</td>
</tr>
</tbody>
</table>

Results are expressed as mean and standard deviations unless otherwise specified. Effect size or standardized difference is calculated by dividing the difference of the averages of the two groups by the standard deviation in the total population. Effect size: 0.2 = small difference; 0.5 = medium difference; 0.8 = large difference. BMI: body mass index; ppoFEV₁: predicted postoperative forced expiratory volume in 1 s; ASA: American Society of Anaesthesiology score; ECOG: Eastern Cooperative Oncology Group performance score; CAD: coronary artery disease.
American College of Chest Physicians guidelines [6, 7]. However, as stated before these studies were conducted at a time when lung resections were performed mostly via a thoracotomy. There is a lack of data regarding low VO2 max and VAT lobectomies. Our aim of this study was to confirm the relationship between VO2 max and morbidity and mortality following a lobectomy and to establish if this relationship holds true for lobectomies performed via the VATS approach.

Main findings

Although we found a reduced morbidity rate after VATS compared with thoracotomy even in the patients with high VO2 max, the greatest benefit of VATS was observed in those patients with a low VO2 max.

The cardiopulmonary morbidity and mortality rates were 2- and 5-fold lower following VAT lobectomy compared with thoracotomy, respectively.

Matched comparison of the thoracotomy patients showed that low VO2 max was associated with an increased mortality rate following lung resection, confirming previous reports [2, 4, 5].

Conversely, matched comparison of the VATS patients demonstrated that morbidity and mortality rates of patients with low VO2 max were similar to those of patients with higher VO2 max.

Our findings confirmed recent evidence showing a protective effect of VATS in high-risk patients [11–14]. One particular study by Demmy and Curtis [13] compared VATS versus open lobectomy in patients with unfavourable risk factors. They classified patients as high risk based on preoperative FEV1 <50% predicted. They demonstrated that despite the fact that there was a higher proportion of patients with unfavourable risk factors in the VATS group; VATS resulted in reduced length of stay, shorter chest tube durations and earlier returns to full preoperative activity.

In a recent analysis from the Society of Thoracic Surgeons General Thoracic database, Burt et al. [14] found that in patients with ppoFEV1% <40%, mortality was 7-fold higher in the open group (4.8%) compared with the matched VATS group (0.7%, P = 0.003). Likewise, in patients with a ppoDLCO% <40%, mortality was significantly higher in the thoracotomy group compared with the VATS group (5.2% open vs 2.0% VATS, P = 0.003). The same trend was observed regarding cardiopulmonary complications, which were shown to be higher in the high-risk thoracotomy group compared with the high-risk VATS group.

Berry et al. [11] confirmed that DLCO and FEV1 remained significant predictors of pulmonary morbidity only when operating via a thoracotomy. They did not correlate with morbidity in patients undergoing a VAT lobectomy.

Most recently, Falcoz et al. [23] performed an ESTS database subgroup analysis comparing outcome after lobectomy performed through VATS versus thoracotomy. They found a significant reduction of cardiopulmonary complications after VATS compared with thoracotomy in several subsets of high-risk patients (elderly, low BMI, ASA grade >2 and ppoFEV1 <40%).

Our results appear in line with the previously reported evidence, showing a benefit of VATS in high-risk patients. The main difference is the methodology used to define the subset of patients at increased risk. In fact, while the previous investigations mainly used pulmonary thresholds, we applied VO2 max as this is regarded the global parameter to assess the whole oxygen transport system. In this regard, our results add to the existing literature and challenge current operability criteria. The use of VATS may allow the inclusion of more patients for surgery by lowering the level of surgical risk.

Limitations

The current study may have several potential limitations. This is an analysis of data registered on a large multi-institutional database. Submission of data to the database is voluntary and the accuracy of the data is reliant on the individuals contributing to it. At present, data from only a small fraction of the units participating in the ESTS Institutional Accreditation Program has been validated for quality and consistency with the data source. Therefore, the majority of data have not been centrally audited and this needs to be taken into consideration when interpreting the results from organizational databases of this scale.

Furthermore, as this is a generic database it lacks certain details that are pertinent to VAT lobectomy: the rate of conversion, whether the converted cases were classed as VATS and the number of ports used, etc. Analgesia regimes and pain scores are not currently recorded in the ESTS database and would be very difficult to standardize across so many institutions. Therefore, it is impossible to determine whether the effect we are seeing is the result of lower postoperative pain. A specific VAT lobectomy section is under development within the ESTS database committee for a more accurate analysis of this procedure.

The results of this analysis may be affected by small numbers as only a minority of patients in the database had VO2 max available. In particular, only 72 patients submitted to VAT lobectomy had a low VO2 max. This prevented us to test lower thresholds of VO2 max (i.e. 10–12 ml/kg/min), which may have been more predictive of complications but which would have restricted even more the sample size.

Although propensity score is the most rigorous method to minimize the selection bias in a non-randomized setting, it cannot completely account for unknown variables affecting the outcome that are not correlated strongly with the measured variables.

Finally, the use of complications for outcome analysis, particularly when recorded in a large multicentre database, may represent a critical aspect. Problems of under-reporting or miscoding are a well-known limitation especially when complications are imputed by multiple end-users. Nevertheless, complications were well defined at the outset of the database and definition were published annually in the Database Report.

CONCLUSIONS

The results of our analysis indicate that low VO2 max is not associated with increased morbidity and mortality in patients undergoing a VAT lobectomy. Approximately one-third of candidates for lung resection for lung cancer displayed a preoperative value of VO2 max below 15 ml/kg/min. Our findings challenge traditional operability criteria and can be used as an additional information during patient counselling and as an aid in the shared decision-making process.

Conflict of interest: none declared.
REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr G. Varela (Salamanca, Spain): I agree that the VATS approach is associated with a lower rate of complications compared to open. You have tested the hypothesis that this protective effect is also seen in patients with a VO2 max under 15 ml/kg/min. There are some possible confounding factors in your data. In the ESTS database, VATS is considered only if no rib spreader is used and, under the term ‘thoracotomy’, different types are included: the classic posterolateral, axillary, and muscle-sparing posterior or lateral. According to some papers in the literature, axillary mini-thoracotomy is followed by a statistically lower rate of complications compared to posterolateral. I wonder how these facts could influence your results?

Dr Begum: As you said, in the database it’s very difficult to determine what type of thoracotomy patients have had. However, there was a publication last year by Andreotti et al. which looked at VATS versus mini-thoracotomy. Although they didn’t look at the morbidity and mortality, they looked at pain scores, and they found that patients who underwent a VATS lobectomy still had lower pain at 1, 12, 24 and 48 h following surgery.

Dr Varela: A second confounder in your data could be the different types of perioperative care in different units. Intensive physiotherapy has a protective effect in decreasing the rate of pulmonary complications. Can you comment on that?

Dr Begum: I acknowledge that this is a limitation of our dataset and it doesn’t contain data regarding postoperative care and whether or not these patients went on to intensive care or high dependency care, and a further, more detailed study is required.

Dr Varela: You conducted a propensity score-matched analysis, matching patients with low VO2 max or high VO2 max. I took the liberty of comparing your patients with low VO2 max undergoing VATS or thoracotomy. I arranged your cases on a 2 × 2 table, and the odds ratio I found was 1.2 with a confidence interval of 0.4 to 4.3. There is no significant difference if you consider only patients with VO2 max under 15.

Dr Begum: I acknowledge that that’s the case, but our dataset is limited by the small number of patients we have with a low VO2 max in the database. And I think if we actually tested patients with a lower VO2 max, say, of 10 ml/kg/min, we may find that the data is more significant. It is difficult to do this with such small numbers.

Dr E. Lim (London, UK): I think in Europe we must move away from VO2 max for risk assessment. Our attitude and thinking are wrong. We should stop studying saying that low VO2 max is associated with higher mortality. I accept that. Everything shows that. The point in question is, what is your survival from cancer if you have a low VO2 max, if you have an operation; the answer from CALGB suggests that your survival will be twice as long. So my comment is, please, stop using VO2 max as a risk assessment. It means nothing.

My second point is, do you think the results of VATS lobectomy could be a reflection of the fact that the VATS surgeons were choosing patients with otherwise lower stage, although their VO2 max was lower, with fewer comorbidities, smaller tumours, and that the excellence of the VATS technical surgeons could have made the difference rather than the access, which is VATS itself?

Dr Begum: So you are suggesting that the patients have been sub-selected so that they are earlier stage?

Dr Lim: Yes.

Dr Begum: It is difficult to determine whether or not this is the case. Obviously VATS lobectomy can only be performed up to a certain stage of tumour. But we have compared like with like here, so tumour sizes have been matched. So I do not think that this should be a confounding factor in this study.