Original Article

An Alternative Method for Predicting the Risk of Postoperative Complications in Lung Resection

Maria del Carmen Vargas Fajardo, a Nuria María Novoa Valentín, b, ∗ Marcelo Fernando Jiménez López, b Jacinto Ramos Gonzalez, c Gonzalo Varela Simó b

a Servicio de Anestesiología, Hospital Universitario de Salamanca, Salamanca, Spain
b Servicio de Cirugía Torácica, Hospital Universitario de Salamanca, IBSAL, Salamanca, Spain
c Servicio de Neumología, Unidad de Pruebas Funcionales Respiratorias, Hospital Universitario de Salamanca, Salamanca, Spain

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ABSTRACT

Objectives: The aims of this study were to design a best fit linear regression model to estimate VO2 max (estimated VO2) and to compare the ability of VO2 values (measured and estimated) predicting cardiorespiratory complications in a series of patients undergoing lung resection for lung cancer.

Method: This was a prospective, observational study performed in 83 patients. Variables analyzed were: demographic characteristics, comorbidity, body mass index (BMI), FEV1%, FVC, diffusion capacity (DLCO%), mean daily distance walked in kilometers, VO2 max measured by cardio-pulmonary exercise test (CPET) and postoperative complications. Descriptive and comparative statistical analysis of the variables was performed using the Mann–Whitney test for categorical variables and the Student's t-test for continuous variables. A new linear regression model was designed, where the dependent variable (measured VO2 max) was estimated by the distance, DLCO% and age, resulting in the estimated VO2. The predictive power of the measured and estimated consumption was analyzed using the Student's t-test, grouping by the occurrence or absence of cardiorespiratory complications.

Results: Both groups were homogeneous for age, sex, BMI, FEV1%, DLCO%, comorbidity, type of resection performed and mean distance walked per day. Estimated VO2 and measured VO2 were normally distributed (K–Smirnov test, P>0.32). VO2 means estimated by the model (age, DLCO% and mean distance walked per day) were significantly different between patients with and without complications (Student’s t-test, P=0.037) compared with measured VO2 values, which did not differentiate groups (Student’s t-test, P=0.42).

Conclusion: The VO2 max estimated by the model is more predictive in this case series than the VO2 max measured during a standard exercise test.

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Un método alternativo para la predicción del riesgo de complicaciones postoperatorias en la resección pulmonar

RESUMEN

Objetivos: Los objetivos de este trabajo son rediseñar un modelo de regresión lineal para estimar el valor de VO2 max (VO2 estimado) ya publicado y comparar la capacidad predictiva de los valores VO2 medido y VO2 estimado en la aparición de complicaciones cardiorespiratorias en una serie de pacientes sometidos a resección pulmonar por cáncer de pulmón.

Método: Estudio prospectivo y observational en 83 pacientes. Variables analizadas: demográficas, comorbilidad, IMC, FEV1%, FVC%, DLCO%, distancia recorrida media diaria (km), VO2 max medido en el test de ejercicio cardiopulmonar (CPET) y complicación postoperatoria. Estadística descriptiva y comparativa de
variables usando Mann-Whitney test para categorías y t de Student para continuas normales. Se diseña un modelo de regresión lineal donde VO$_{2\max}$, la variable dependiente, se estima desde la distancia recorrida, DLCO% y edad del paciente y su resultado es la VO$_2$ estimada. Se compara la capacidad predictiva de los VO$_{2\max}$ medido y estimado mediante t de Student, agrupando por ocurrencia o no de complicaciones cardiorespiratorias.

Resultados: Los 2 grupos son homogéneos en edad, distribución de sexos, IMC, FEV1%, DLCO%, comorbilidad, cirugía realizada y distancia media recorrida/día. VO$_2$ medida y VO$_2$ estimada tienen distribución normal (K-Smirnov p > 0,32). En la predicción de complicaciones, las medias del VO$_2$ estimado a partir del modelo son significativamente diferentes entre los pacientes con/sin complicación (t de Student p = 0,037); frente a los valores de VO$_2$ medido que no distinguen grupos (t de Student p = 0,42).

Conclusiones: El VO$_{2\max}$ estimado por el modelo es más predictivo en esta serie de casos que el VO$_{2\max}$ medido en una CPET.
stay. Complications were grouped into those of cardiac, respiratory or technical nature.

**Study Variables**

All variables were prospectively collected in a computerized database:

- **Patient variables:** age, gender, body mass index (BMI), forced vital capacity (FVC), %FEV<sub>1</sub> and %DLCO (with optimized bronchodilator treatment, if necessary); comorbidities: systemic hypertension (HT), ischemic cardiovascular disease, diabetes mellitus (DM), chronic renal failure (creatinine >2 mg/dl), cardiac valve disease, and/or chronic arterial disease.
- **CPET variables:** patient–weight adjusted VO<sub>2peak</sub> (ml/kg/min) in absolute values and percentage.
- **Pedometer variables:**
  - Total number of steps per day or “total steps”.
  - Number of aerobic steps per day or “aerobic steps”. This count activates when the wearer has walked over 10 min at a minimum rate of 60 steps per minute and inactivates if the wearer rests for more than 1 min.
  - Ambulatory activity time in minutes per the day or “time”, divided into total activity and aerobic activity.
  - Distance traveled during daily activity in kilometers or “distance”.
- **Postoperative complications:**
  - Respiratory: lobar/pulmonary atelectasis, pneumonia according to Center for Disease Control/National Healthcare Safety network criteria,<sup>10</sup> persistence of respiratory failure at discharge (PO<sub>2</sub>&lt;60 mmHg or PCO<sub>2</sub>&gt;45 mmHg), need for mechanical ventilation at any time after extubation in the operating room, and occurrence of pulmonary thromboembolism.
  - Cardiovascular: occurrence of stroke, arrhythmia (auricular fibrillation, AF), myocardial ischemia or acute myocardial infarction, and heart failure.
  - Technical: need for reoperation for massive hemothorax, occurrence of prolonged air leak or bronchial fistula within the first week after resection.

**Statistical Method**

Descriptive and comparative statistical analysis of the study variables was performed. After a correlation analysis between variables, a linear regression model was designed, where VO<sub>2max</sub> was the dependent variable, and the variables distance traveled, %DLCO and patient age were set as independent variables. The outcome variable in this model was estimated VO<sub>2</sub>. Bootstrap technique with 1000 replications was performed to study collinearity and perform resampling, in order to obtain a more robust standard error of the coefficients values. Finally, occurrence of postoperative morbidity and mortality and their relationship with VO<sub>2max</sub> values, both the measured values and the values estimated with the predictive model developed, were analyzed using paired Student’s t-test. These analyses were performed using the statistical software Stata 10.0.

**Results**

**Final Study Population**

The final study population was 83 patients, of whom 15 were women (18.1%). Population age was 64.59±9.5 (38–80 years). Twenty patients (24.1%) were being treated for hypertension, 18 (21.7%) met criteria for COPD and were receiving bronchodilators, nine (10.8%) had DM, six (7.2%) significant peripheral artery disease, five (6%) stable ischemic heart disease, and one patient (1.2%) had renal failure not needing dialysis but strict medication adjustments. None of the patients had associated valvular pathology. Patients wore the pedometer for an average of 25 days (range 5–41 days) (Table 1), showing a routine in the schedules and time periods they usually walked. All patients performed the CPET according to protocol.

Seventeen typical segmentectomies, 61 lobectomies, three pneumonectomies and two bilobectomies (one right and one left) were performed.

There was no mortality in this series. In terms of morbidity, 26 patients (31.3%) experienced a complication: eight (9.6%) were respiratory, one (1.2%) was a cardiac complication (arrhythmia), two patients had concomitant cardiac and respiratory complications, and 15 patients experienced technical complications (18.1%), mainly prolonged air leak.

**Preliminary Design Correlations and Linear Regression Model**

We analyzed the possible correlations between the recorded lung function variables and aerobic activity with VO<sub>2max</sub> and VO<sub>2peak</sub> data.

In this series, VO<sub>2max</sub> was significantly associated with age (r=-0.451, P=0.000), BMI (r=-0.357, P=0.001), DLCO (r=0.238, P=0.030), number of total steps/day (r=0.278, P=0.011), and distance traveled/day (r=0.315, P=0.004), but not with %FEV<sub>1</sub> (r=0.182, P=0.1), presence of COPD (r=0.088, P=0.431), aerobic steps/day (r=0.151, P=0.173) or the total time of aerobic activity (r=0.117, P=0.294).

%VO<sub>2</sub> was significantly correlated only with %FEV<sub>1</sub> (r=0.303, P=0.006), DLCO (r=0.390, P=0.000), and the number of total steps/day (r=0.244 steps, P=0.027).

After analyzing the correlations between variables, the final linear regression model with VO<sub>2max</sub> and %VO<sub>2</sub> as dependent variables included those variables with the highest correlation with the dependent variable and showing no collinearity between them.

Of the models developed for %VO<sub>2</sub> and for VO<sub>2max</sub>, the best fitting was related to the estimated VO<sub>2max</sub> values (dependent variable) and included as independent variables age, DLCO and distance traveled (Table 2). Discriminant analysis for collinearity was performed and none of the variables were related to the others (collinearity index <15 in all variables).

**Population Analysis According to Occurrence of Postoperative Cardiac Complications**

The two groups into which the population was divided were homogeneous (Table 3).

Both variables (measured and estimated VO<sub>2</sub>) were normally distributed (K-Smirnov P=32).

As for prediction of complications, mean estimated VO<sub>2</sub> according to the model was significantly different between patients with/without complication (P=0.037), compared to measured VO<sub>2</sub> values, which did not distinguish these groups (P=.42) (Table 4 and Fig. 1).

**Discussion**

The main objective of this study was to design a method for predicting the patient’s VO<sub>2</sub> from variables easily obtained in all patients, and to analyze its predictive capacity for the occurrence of cardiac complications after lung resection.

The model developed had R<sup>2</sup>=0.94, meaning a very good fit. The three variables included are age, %DLCO and average distance traveled per day. The inverse relationship between age and VO<sub>2</sub> is well known,<sup>11</sup> and inclusion of this variable into the analysis improves
Table 1
Characteristics of Pedometer-recorded Activity and CPET-measured Oxygen Consumption by Study Population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedometer activity data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total steps</td>
<td>821.6</td>
<td>20,471.4</td>
<td>9508.83</td>
<td>4665.32</td>
</tr>
<tr>
<td>Aerobic steps</td>
<td>0</td>
<td>10,904.5</td>
<td>3688.47</td>
<td>2989.35</td>
</tr>
<tr>
<td>Time (min)</td>
<td>0</td>
<td>108.5</td>
<td>35.66</td>
<td>27.78</td>
</tr>
<tr>
<td>Distance (km)</td>
<td>0.37</td>
<td>12.87</td>
<td>5.82</td>
<td>3.19</td>
</tr>
<tr>
<td>Measured VO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂ (ml/kg/min)</td>
<td>10.8</td>
<td>31.2</td>
<td>18.79</td>
<td>4.32</td>
</tr>
<tr>
<td>VO₂ (%)</td>
<td>48</td>
<td>116</td>
<td>78.54</td>
<td>15.39</td>
</tr>
</tbody>
</table>

Table 2
Characteristics of the Best Fit Linear Regression Model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald test</th>
<th>Significance</th>
<th>β</th>
<th>95% CI of β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>4.49</td>
<td>0.000</td>
<td>0.398</td>
<td>0.066–0.170</td>
</tr>
<tr>
<td>DLCO</td>
<td>4.25</td>
<td>0.007</td>
<td>0.414</td>
<td>0.054–0.148</td>
</tr>
<tr>
<td>Distance</td>
<td>3.19</td>
<td>0.002</td>
<td>0.186</td>
<td>0.204–0.286</td>
</tr>
</tbody>
</table>

R²=0.940; P<.001.

the result. Both %DLCO adjusted for the patient's hemoglobin and the average distance traveled per day in kilometers were already part of the previously published model. Inclusion of these two variables represented an innovation in the variables that had been used to estimate the VO₂ in other studies. In this analysis, as in the previous one, we chose to use the variable “distance” instead of “total steps” because its correlation index with VO₂ was better (r=0.315 vs r=0.278). There are two reasons for including %DLCO: first, this parameter proved to be correlated with age (r=0.245) and VO₂max (r=0.238) and, second, because %DLCO is an accepted independent predictor of postoperative complications.

The second objective was to analyze the predictive ability of these two variables of oxygen consumption: the measured one and the estimated one. In our analysis, predictive ability is significantly better in the estimated model. Analyzing the performance of average values in the different groups, two aspects draw attention (Table 4 and Fig. 1): first, the difference between groups with/without complication is very small in both measurements; second, measured VO₂ has very similar values, and non-discriminating between the two groups because the ranges of measurements are very wide, unlike estimated VO₂ values whose ranges are much narrower and probably confer a predictive advantage. A recent meta-analysis of Benzo et al. including 14 studies with 955 subjects found that patients with postoperative complications had significantly lower oxygen consumption than those who did not. However, average difference was only 3 ml/kg/min or 8.95%

Table 3
Comparison of Occurrence of Postoperative Cardiac Complications (CR) in the Two Study Subpopulations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Without CR Complications (n=72)</th>
<th>Patients With CR Complications (n=11)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male</td>
<td>57 (79)</td>
<td>11 (100)</td>
<td>.201</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (25)</td>
<td>2 (18.2)</td>
<td>.055</td>
</tr>
<tr>
<td>COPD</td>
<td>13 (18.05)</td>
<td>5 (45.5)</td>
<td>.178</td>
</tr>
<tr>
<td>DM</td>
<td>8 (11.1)</td>
<td>1 (9.1)</td>
<td>.01</td>
</tr>
<tr>
<td>IHD</td>
<td>5 (6.9)</td>
<td>0</td>
<td>.08</td>
</tr>
<tr>
<td>Arterial disease</td>
<td>4 (5.5)</td>
<td>2 (18.2)</td>
<td>.098</td>
</tr>
<tr>
<td>RF</td>
<td>1 (1.4)</td>
<td>0</td>
<td>.06</td>
</tr>
</tbody>
</table>

Mean (DE)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (DE)</th>
<th>Mean (DE)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.8 (9.3)</td>
<td>69.2 (8.8)</td>
<td>.08</td>
</tr>
<tr>
<td>IMC</td>
<td>26.7 (4.7)</td>
<td>23.9 (4.3)</td>
<td>.78</td>
</tr>
<tr>
<td>%FEV₁</td>
<td>85.1 (20.3)</td>
<td>77.5 (24.5)</td>
<td>.26</td>
</tr>
<tr>
<td>%FVC</td>
<td>96.4 (19.1)</td>
<td>100.2 (19.1)</td>
<td>.53</td>
</tr>
<tr>
<td>%DLCO</td>
<td>78.2 (20.1)</td>
<td>66.78 (20.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Total footsteps</td>
<td>9511.2 (4701.3)</td>
<td>9493.2 (4641.5)</td>
<td>.99</td>
</tr>
<tr>
<td>Aerobic footsteps</td>
<td>3750.6 (2921.1)</td>
<td>3281.5 (3533.5)</td>
<td>.63</td>
</tr>
<tr>
<td>Time</td>
<td>36.1 (26.9)</td>
<td>32.6 (34.2)</td>
<td>.69</td>
</tr>
<tr>
<td>Distance</td>
<td>5.9 (3.2)</td>
<td>4.9 (3.03)</td>
<td>.349</td>
</tr>
</tbody>
</table>

Table 4
Numerical Values of Mean Oxygen Consumption by Groups According to Occurrence of Cardiopulmonary Complications (CR).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured VO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without CR</td>
<td>72</td>
<td>18.78</td>
<td>4.42</td>
<td>17.7–19.8</td>
<td>.42</td>
</tr>
<tr>
<td>With CR</td>
<td>11</td>
<td>18.85</td>
<td>3.83</td>
<td>16.2–21.4</td>
<td></td>
</tr>
<tr>
<td>Estimated VO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without CR</td>
<td>72</td>
<td>18.87</td>
<td>2.28</td>
<td>18.3–19.4</td>
<td>.037</td>
</tr>
<tr>
<td>With CR</td>
<td>11</td>
<td>17.35</td>
<td>1.7</td>
<td>16.1–18.5</td>
<td></td>
</tr>
</tbody>
</table>
The authors concluded from this analysis that patients with consumption over 20 ml/kg/min had a very low complication rate. This did not mean that complications would not occur, only that in case of occurrence, they had a better chance of survival. Interestingly, the range of values of measured VO₂ in patients who experienced complications in our study was higher than in those who did not (17.7–19.8 vs 16.2–21.4) and mean values were similar (18.75 vs 18.85; P=0.42). However, the ranges of estimated consumption values were less wide (18.3–19.4 vs 16.1–18.5) and means were significantly different (18.87–17.35; P=0.037). In the meta-analysis, the lower threshold associated with a high complication rate is 16 ml/kg/min, and this is 17.35 ml/kg/min in our patients, slightly higher but within the range of values published in studies analyzed.

Although the comparison of the characteristics of these two subpopulations of patients—those who experience complications and those who do not—yields two statistically similar groups, patients who experience more complications have older mean age (63.8–69.2 years) and lower %DLCO (78.2–66.7). These data are consistent with published results regarding patients who experience complications in other series. Current clinical guidelines for the evaluation of patients eligible for lung resection recommend a final decision based on the CPET results, i.e., according to the VO₂max reached expressed as absolute values or percentage (%VO₂).

The values on which VO₂max depends include age, gender, previous respiratory disease, genetic characteristics, and the training degree of the patient, among other factors. The training degree is in turn is strongly linked to daily physical activity, his/her health status, and mortality, and may be useful for predicting postoperative adverse events. In this regard, our group has sought an alternative to estimate VO₂max value by studying performance at an easy exercise.

Recent studies confirm the existence of numerous shortcomings in the implementation of the European functional assessment algorithm published in 2009. The major difficulty is conducting high-technology stress testing, since only 84% of operated patients underwent this for various reasons. The same guidelines recognize that the standardized symptom-limited stair climbing test can be an alternative to performing the CPET, helping reduce the number of patients who would require the latter. However, this test has been criticized for its poor standardization and difficulty for performance in a safe place for the patient. In addition, many patients have joint and insecurity problems when climbing stairs, so results can sometimes be suboptimal, as occurs with the CPET, in which some unsatisfactory results may be attributable to the harsh conditions required for its performance.

Patient limitations are one of the root causes for not being able to perform the CPET. Cardiovascular contraindications and joint limitations are especially relevant in an increasingly older population, with more associated comorbidity. Overcoming this limitation is difficult, but possibly the solution lies in the development of new simple and safe strategies to measure the exercise capacity of a given patient. This is the case of measurements based on walked distance or the quality of daily exercise that the patient performs in everyday life.

It is not the intention of this study to question the predictive value of the CPET in surgical risk evaluation. At present, the measurement of daily physical activity is not considered a substitute for the formal CPET, but further studies with larger series and patients more functionally compromised might allow may support this as a valid, cost-saving and effective screening test for those patients in which a formal CPET cannot be conducted due to contraindication or limitation, or also as an alternative when CPET is not available in the center.

Our study has some important limitations. On the one hand, the limitation derived from its sample size, which limits the possibilities for statistical study. This reason prevented a division of the sample into two groups: one to create the mathematical model and a second group to assess validity. Analysis of larger series in the future will enable testing of the reliability of the conclusions drawn in this study. This aspect also influences the number of cardiac complications included in the study, experienced by only 11 patients, which also limits the ability to extrapolate the results. Another important limitation of this study is a possible observation bias. The data collected were generated by the patient during everyday life outside the hospital. Therefore, it is not possible to be absolutely certain that this person was wearing the pedometer. However, in order to reduce this bias, special emphasis was made to each patient during consultation on the importance of not letting anyone else from his/her environment use the pedometer. Lastly, the findings may be affected by case-selection bias, since it was not possible to obtain data from patients who were not considered candidates for surgery, thereby not eligible for this study, due to the selection criteria of the physicians who refer patients to our unit.

In conclusion, the VO₂ value of a given patient can be reliably estimated from age, %DLCO and average walking distance per day, measured with a pedometer. In this series, estimated VO₂max was more predictive of the occurrence of cardiac complications than VO₂max measured in a standard exercise test. Our next objective will be the validation of this model in a larger series and with a broader patient profile.

Conflicts of Interest
The authors declare no conflict of interest that might cause a bias in this study.

References