ARCHIVOS DE BRONCONEUMOLOGIA

Original Article

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

Maria del Carmen Vargas Fajardo,[a] Nuria Maria 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*

ARTICLE INFO

ABSTRACT

Objectives: The aims of this study were to design a best fit linear regression model to estimate VO$_{2max}$ (estimated VO$_2$) and to compare the ability of VO$_2$ 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, VO$_{2max}$ 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 VO$_{2max}$) was estimated by the distance, DLCO% and age, resulting in the estimated VO$_2$. 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 VO$_2$ and measured VO$_2$ were normally distributed (K–Smirnov test, *P*>.32). VO$_2$ 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*=.037) compared with measured VO$_2$ values, which did not differentiate groups (Student's *t*-test, *P*=.42).

Conclusion: The VO$_{2max}$ estimated by the model is more predictive in this case series than the VO$_{2max}$ measured during a standard exercise test.

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 VO$_{2max}$ (VO$_2$ estimado) ya publicado y comparar la capacidad predictiva de los valores VO$_2$ medido y VO$_2$ estimado en la aparición de complicaciones cardiorrespiratorias en una serie de pacientes sometidos a resección pulmonar por cáncer de pulmón.

Método: Estudio prospectivo y observacional en 83 pacientes. Variables analizadas: demográficas, comorbilidad, IMC, FEV1%, FVC%, DLCO%, distancia recorrida media diaria (km), VO$_{2max}$ medido en el test de ejercicio cardiopulmonar (CPET) y complicación postoperatoria. Estadística descriptiva y comparativa de

variables usando Mann-Whitney test para categóricas y t de Student para continuas normales. Se diseña un modelo de regresión lineal donde VO_{2max}, 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_{2max} medido y estimado mediante t de Student, agrupando por ocurrencia o no de complicaciones cardiorrespiratorias.

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_{2max} estimado por el modelo es más predictivo en esta serie de casos que el VO_{2max} medido en una CPET.

Introduction

Despite the refinement and adaptation of published algorithms and mathematical decision models,[1] prediction of surgical risk is difficult due to selection bias inherent to these models.[2] Comprehensive assessment of the cardiorespiratory system using standardized exercise tests provides a lot of information about the physiological status of the patient who is to undergo pulmonary resection.[3] Calculation of peak exercise oxygen consumption (VO_{2max})[4] is considered the most reliable test to quantify individual risk for postoperative complications. However, this technique is not available in all centers performing lung surgery, and it cannot be applied in all patients.[5] The reasons are physical or medical contraindications, or structural problems in hospitals where it is implemented.

Among other options, performance at symptom-limited stairclimbing test has shown the best correlation with surgical morbidity,[6] although its poor standardization and the difficulty for performing the test in a safe environment for the patient prevent routine use.

A previous study seeking possible alternatives[7] found a correlation between VO_{2max} values measured by standard cardiopulmonary exercise test (CPET) and VO_{2max} values estimated with a regression model that included measurement of average distance (km) the patient walked each day, collected with a pedometer during the preoperative waiting period, and carbon monoxide diffusing capacity (%DLCO) adjusted for the patient's hemoglobin levels.

The objectives of the present study were to improve the previously designed linear regression model, in order to find the best correlation between oxygen consumption values (measured VO_2 and estimated VO_2), and to compare the ability of these two variables to predict the occurrence of cardiac complications in a series of patients undergoing anatomic pulmonary resection for lung cancer.

Methods

We conducted a prospective, observational study of repeated measures for each subject before and after lung resection.

Study Population

Ninety-five patients were initially included in the study, of which 12 were excluded due to inability to perform exercise testing because of joint problems that prevented smooth pedaling (*n*=7), vascular comorbidity (presence of aorta aneurysm and recent treatment for deep venous thrombosis; *n*=2), a vasovagal episode prior to the exercise test (*n*=1) or because of technical issues with the pedometer that prevented correct measurement of ambulatory activity (*n*=2).

The final sample included 83 consecutive patients with non-small-cell lung cancer scheduled for major anatomic lung resection (typical segmentectomy, lobectomy, bilobectomy or pneumonectomy) from May 2009 to December 2011, who agreed to be included in the study and signed informed consent. All patients who, due to limitation or contraindication, were not able to properly perform the CPET were excluded. Inclusion of patients with ischemic heart disease was conditional on the existence of a previous coronary revascularization or evidence of good functional capacity, demonstrated by exercise testing or equivalent examination.

The criteria for operability in this study have been previously published[8]: absence of a comorbidity of worse prognosis than cancer, Karnofski index >50%, estimated postoperative forced expiratory volume in one second (FEV_1) greater than 30%, and estimated postoperative DLCO greater than 40%.

All patients were treated by the same multidisciplinary team and operated via axillary thoracotomy without muscle section, in which a 2-cm auxiliary incision was also performed.

Measurement of Maximum Oxygen Consumption

Cardiopulmonary exercise testing was carried out in the Respiratory Functional Test laboratory using the cardiopulmonary exercise test module (ergospirometry) MasterScreen CPX Jaeger-Vyasis-Healthcare, which enables the measurement of ventilatory parameters, VO_2, carbon dioxide production (VCO_2), anaerobic threshold, respiratory exchange ratio (RER), heart rate (HR), ventilatory equivalent for oxygen (EQO_2), and ventilatory equivalent for CO_2 ($EQCO_2$) in an open "breath-by-breath" type system.

The CPET modality used in our center is the symptom-limited incremental exercise test. In this modality, the patient performs exercise on a bicycle ergometer with continuous load increases over a period of about 10 min (according to Wasserman protocol).[9]

Measurement of Daily Physical Activity by Pedometer

An OmronWalking Style Pro HJ-720IT-E2 pedometer was used with the Bi-Link downloadable software specific to this supplier.

In the first visit, the pedometer the patient would use until the day of surgery was programmed with the date, time and footstep length. Participating in this study did not involve lengthening the preoperative waiting time.

For analysis, the activity recorded by pedometers was reviewed on a case-by-case and day-to-day basis, excluding from the calculation of parameter means those days without any registered activity because the patient did not use the pedometer.

Postoperative Complications

Data on the type of surgery, occurrence of postoperative complications and type of complications were collected during hospital

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$_1$ 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$_{2peak}$ (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,[10] persistence of respiratory failure at discharge (PO$_2$<60 mmHg or PCO$_2$>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$_{2max}$ 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$_2$. 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$_{2max}$ 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$_{2max}$ and VO$_{2peak}$ data.

In this series, VO$_{2max}$ was significantly associated with age ($r=-0.451$, $P=.000$), BMI ($r=-0.357$, $P=.001$), DLCO ($r=0.238$, $P=.030$), number of total steps/day ($r=0.278$, $P=.011$), and distance traveled/day ($r=0.315$, $P=.004$), but not with %FEV$_1$ ($r=0.182$, $P=.1$), presence of COPD ($r=0.088$, $P=.431$), aerobic steps/day ($r=0.151$, $P=.173$) or the total time of aerobic activity ($r=0.117$, $P=.294$).

%VO$_2$ was significantly correlated only with %FEV$_1$ ($r=0.303$, $P=.006$), DLCO ($r=0.390$, $P=.000$), and the number of total steps/day ($r=0.244$ steps, $P=.027$).

After analyzing the correlations between variables, the final linear regression model with VO$_{2max}$ and %VO$_2$ 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$_2$ and for VO$_{2max}$, the best fitting was related to the estimated VO$_{2max}$ 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$_2$) were normally distributed (K–Smirnov $P>.32$).

As for prediction of complications, mean estimated VO$_2$ according to the model was significantly different between patients with/without complication ($P=.037$), compared to measured VO$_2$ 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$_2$ 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 $R^2=0.94$, 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$_2$ is well known,[11] and inclusion of this variable into the analysis improves

Table 1
Characteristics of Pedometer-recorded Activity and CPET-measured Oxygen Consumption by Study Population.

Variable	Minimum	Maximum	Mean	Standard Deviation
Pedometer activity data				
Total steps	821.6	20 471.4	9508.83	4665.32
Aerobic steps	0	10 904.5	3688.47	2989.35
Time (min)	0	108.5	35.66	27.78
Distance (km)	0.37	12.87	5.82	3.19
Measured VO_2				
VO_2 (ml/kg/min)	10.8	31.2	18.79	4.32
VO_2 (%)	48	116	78.54	15.39

Table 2
Characteristics of the Best Fit Linear Regression Model.

	Wald test	Significance	β	95% CI of B
Age	4.49	0.000	0.398	0.066–0.170
DLCO	4.25	0.007	0.414	0.054–0.148
Distance	3.19	0.002	0.186	0.204–0.286

$R^2=0.940$; $P<.001$.

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.[7] Inclusion of these two variables represented an innovation in the variables that had been used to estimate the VO_2 in other studies.[12–14] In this analysis, as in the previous one,[7] we chose to use the variable "distance" instead of "total steps" because its correlation index with VO_2 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 VO_{2max} ($r=0.238$) and, second, because %DLCO is an accepted independent predictor of postoperative complications.[15]

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 VO_2 has very similar values, and non-discriminating between the two groups because the ranges of measurements are very wide, unlike estimated VO_2 values whose ranges are much narrower and probably confer a predictive advantage. A recent meta-analysis of Benzo et al.[16] 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.

Variable	Patients Without CR Complications (n=72) n (%)	Patients With CR Complications (n=11) n (%)	P-Value
Gender: male	57 (79)	11 (100)	.201
Hypertension	18 (25)	2 (18.2)	1
COPD	13 (18.05)	5 (45.5)	.055
DM	8 (11.1)	1 (9.1)	1
IHD	5 (6.9)	0	1
Arterial disease	4 (5.5)	2 (18.2)	.178
RF	1 (1.4)	0	1

	Mean (DE)	Mean (DE)	P-Value
Age	63.8 (9.3)	69.2 (8.8)	.08
IMC	26.7 (4.7)	23.9 (4.3)	.78
%FEV$_1$	85.1 (20.3)	77.5 (24.5)	.26
%FVC	96.4 (19.1)	100.2 (19.1)	.53
%DLCO	78.2 (20.1)	66.78 (20.5)	.08
Total footsteps	9511.2 (4701.3)	9493.2 (4641.5)	.99
Aerobic footsteps	3750.6 (2921.1)	3281.5 (3533.5)	.63
Time	36.1 (26.9)	32.6 (34.2)	.69
Distance	5.9 (3.2)	4.9 (3.03)	.349

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

Variable	n	Mean	SD	Range	P-value
Measured VO_2					
Without CR complication	72	18.78	4.42	17.7–19.8	.42
With CR complication	11	18.85	3.83	16.2–21.4	
Estimated VO_2					
Without CR complication	72	18.87	2.28	18.3–19.4	.037
With CR complication	11	17.35	1.7	16.1–18.5	
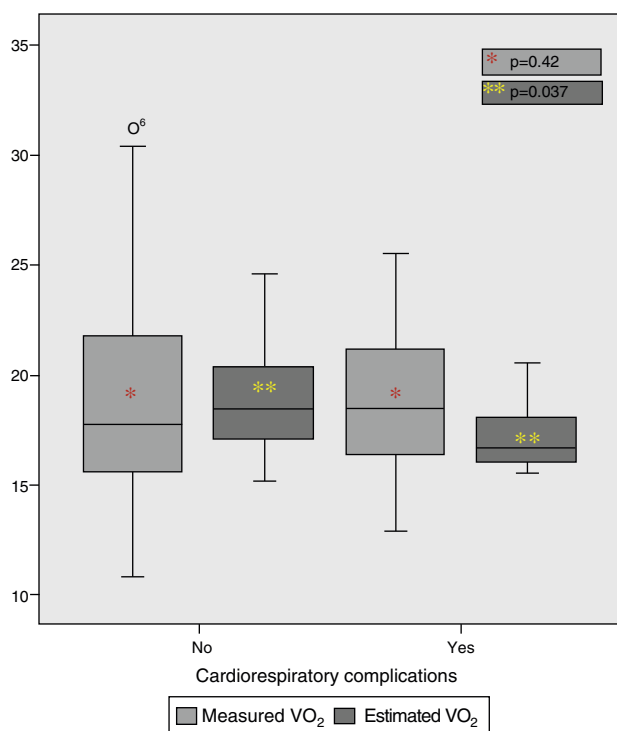
Fig. 1. Differences between VO$_{2max}$ and VO$_2$ mean values, estimated according to the occurrence of postoperative cardiac complications.

between the two groups. 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 VO$_2$ 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=.42). However, the ranges of estimated consumption values are less wide (18.3–19.4 vs 16.1–18.5) and means were significantly different (18.87–17.35; P=.037). In the meta-analysis,[16] 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 the characteristics of patients who experience complications in other series.[16]

Current clinical guidelines[1] for the evaluation of patients eligible for lung resection recommend a final decision based on the CPET results, i.e., according to the VO$_{2max}$ reached expressed as absolute values or percentage (%VO$_2$).

The values on which VO$_{2max}$ depends include age,[11] gender,[17] previous respiratory disease,[18] genetic characteristics,[19] and the training degree of the patient,[17] among other factors. The training degree is in turn is strongly linked to daily physical activity,[20] his/her health status, and mortality,[21,22] and may be useful for predicting postoperative adverse events. In this regard, our group has sought an alternative to estimate VO$_{2max}$ value by studying performance at an easy exercise.

Recent studies[5] confirm the existence of numerous shortcomings in the implementation of the European functional assessment algorithm published in 2009.[1] 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.[7] 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 VO$_2$ 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 VO$_{2max}$ was more predictive of the occurrence of cardiac complications than VO$_{2max}$ 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

1. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. European Respiratory Society and European Society of Thoracic Surgeons joint task force

on fitness for radical therapy. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009;34:17–41.

2. Utley M, Treasure T. The use of scoring systems in selecting patients for lung cancer resection: work-up bias come full-circle. Thorac Surg Clin. 2008;18:107–13.

3. Olsen GN. The evolving role of exercise testing prior to lung resection. Chest. 1989;95:218–25.

4. Brunelli A, Refai M, Xiumé F, Salati M, Sciarra V, Socci L, et al. Performance at symptom-limited stair-climbing test is associated with increased cardiopulmonary complications, mortality, and costs after major lung resection. Ann Thorac Surg. 2008;86:240–7.

5. Novoa NM, Ramos J, Jimenez MF, Gónzalez-Ruiz JM, Varela G. Primera fase de validación del algoritmo europeo de evaluación funcional previa a la resección pulmonar, cuantificación del cumplimiento de las recomendaciones en la práctica clínica real. Arch Bronconeumol. 2012;48:229–33.

6. Toth MJ, Gardner AW, Ades PA, Poehlman ET. Contribution of body composition and physical activity to age-related decline in peak VO$_2$ in men and women. J Appl Physiol. 1994;77:647–52.

7. Novoa NM, Varela G, Jiménez MF, Ramos J. Value of the average basal daily walked distance measured using a pedometer to predict maximum oxygen consumption per minute in patients undergoing lung resection. Eur J Cardiothorac Surg. 2011;39:756–62.

8. Varela G, Cordovilla R, Jimenez M, Novoa N. Utility of standardized exercise oximetry to predict cardiopulmonary morbidity after lung resection. Eur J Cardiothorac Surg. 2001;19:351–4.

9. Wasserman K, Hansen J, Sue D, Stringer W, Whipp B. Clinical exercise testing. In: Weinberg RW, editor. Principles of exercise testing and interpretation including pathophysiology and clinical applications. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 133–59.

10. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36:309–32.

11. Wasserman K, Whipp B. Excercise physiology in health and disease. Am Rev Respir Dis. 1975;112:219–49.

12. Astrand P, Ryhming I. A nomogram for calculation of aerobic capacity from pulse rate during submaximal work. J Appl Physiol. 1954;7:218–21.

13. Zhang K, Werner P, Sun M, Pi-Sunyer FX, Boozer CN. Measurement of human daily physical activity. Obes Res. 2003;11:33–40.

14. Cao Z, Miyatake N, Hihuchi M, Ishikawa-Takata K, Miyachi M, Tabata I. Prediction of VO$_{2max}$ with daily step counts for Japanese adult women. Eur J Appl Physiol. 2009;105:289–96.

15. Ferguson MK, Vigneswaran WT. Diffusing capacity predicts morbidity after lung resection in patients without obstructive lung disease. Ann Thorac Surg. 2008;85:1158–65.

16. Benzo R, Kelley GA, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: a meta-analysis. Respir Med. 2007;101: 1790–7.

17. Woo J, Derleth C, Stratton J, Levy W. The influence of age, gender, and training on exercise efficiency. J Am Coll Cardiol. 2006;47:1049–57.

18. Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. Clin Chest Med. 1994;15:305–26.

19. Ingelsson E, Larson M, Vasan R, O'Donnell C, Yin X, Hirschhorn JN, et al. Heritability, linkage, and genetic associations of exercise treadmill test responses. Circulation. 2007;115:2917–24.

20. Zhang J, Ohta T, Ishikawa-Takata K, Tabata I, Miyashita M. Effects of daily activity recorded by pedometer on peak oxygen consumption (VO$_2$ peak), ventilatory threshold and leg extension power in 30- to 69-year-old Japanese without exercise habit. Eur J Appl Physiol. 2003;90:109–13.

21. Schönhofer B, Ardes P, Geibel M, Köhler D, Jones PW. Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. Eur Respir J. 1997;10:2814–9.

22. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346:793–801.