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Carbon monoxide lung diffusion capacity improves risk stratification in patients without airflow limitation: evidence for systematic measurement before lung resection

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Abstract

Objective: In many centers, carbon monoxide lung diffusion capacity (DLCO) is still not routinely measured in all patients but only in patients with airflow limitation. The objective of the study was to assess the degree of correlation between forced expiratory volume in 1 s (FEV1) and DLCO, and verify whether a low predicted postoperative DLCO (ppoDLCO) could have a role in predicting complications in patients without airflow limitation. **Methods:** We analyzed 872 patients submitted to lung resection between January 2000 and December 2004 in two units measuring systematically DLCO before operation. Correlation between FEV1 and DLCO was assessed in the entire dataset and in different subsets of patients. A number of variables were then tested for a possible association with postoperative cardiopulmonary complications in patients with FEV1 > 80% by univariate analysis. Variables with $p < 0.10$ at univariate analysis were used as independent variables in a stepwise logistic regression analysis (dependent variable: presence of cardiopulmonary morbidity), which was in turn validated by bootstrap analysis. **Results:** The correlation coefficients between FEV1 and DLCO in the entire dataset and in different subsets of lung resection candidates (stratified by age, gender, cause of operation, airflow limitation) were all below 0.5, showing a modest degree of correlation. Two hundred and nineteen of the 508 patients (43%) with FEV1 > 80% had DLCO < 80%. Moreover, in patients with FEV1 > 80%, logistic regression analysis showed that ppoDLCO < 40% was a significant and reliable predictor of postoperative complications ($p = 0.004$). **Conclusion:** The modest correlation between FEV1 and DLCO and the capacity of ppoDLCO to discriminate between patients with and without complications in subjects with a normal FEV1, warrants the routine measurement of DLCO in all candidates for lung resection, irrespective of their FEV1 value, in order to improve surgical risk stratification.

Keywords: Pulmonary function tests; Carbon monoxide lung diffusion capacity; Lung resection; Morbidity

1. Introduction

Carbon monoxide lung diffusion capacity (DLCO) and its corresponding predicted postoperative value (ppoDLCO) are well-recognized predictors of cardiopulmonary morbidity and quality of life after lung resection [1—10].

However, most centers do not perform their measurements systematically in all surgical candidates, confining this examination to selected patients only (i.e., those with an impaired forced expiratory volume in 1 s (FEV1)).

In a recent report from the online European Thoracic Surgery database [11], only 25% of over 3400 lung resection candidates from 27 European centers had DLCO or ppoDLCO performed.

Even commonly accepted functional evaluation guidelines recommended to limit DLCO measurement only in patients with a FEV1 lower than 80% of predicted [12,13].

The approach to select patients for DLCO testing based on their FEV1 values should be warranted only in case of a high correlation between these two variables. However, FEV1 and DLCO reflect the status of two different components of the pulmonary function (airflow and gas exchange), which may be not necessarily correlated between each other.

For this reason, this study was meant to assess the degree of this correlation in different subsets of candidates for lung resection, and to verify whether ppoDLCO could have a role as a predictor of complications in those patients in whom this parameter is not commonly measured (those with a normal FEV1 value).

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2. Methods

We analyzed 872 patients submitted to lung resections (129 wedge/segmentectomy, 611 lobectomy/bilobectomy, 132 pneumonectomy; 639 males and 233 females) between January 2000 and December 2004 at two European Thoracic Surgery units, performing DLCO routinely in all surgical candidates. A small number of patients (20 cases) with missing or unreliable DLCO measurements were excluded from the analysis. All operations were performed for benign (94 cases: 9 emphysema, 5 lobar sequestration, 21 inflammation, 7 fibrosis, 4 aspergilloma, 13 bronchiectasis, 15 hamartoma, 4 tuberculosis, 3 infarction, 2 inflammatory pseudotumor, 2 bronchiolitis obliterans, 2 granulomatosis, 3 round atelectasis, 2 cryptogenic fibrosing alveolitis, 1 pulmonary angiomiolypoma, 1 actinomycosis) or malignant lung diseases (778 cases: 730 primary, 48 metastatic) by certified thoracic surgeons through a muscle-sparing thoracotomy whenever possible, and all patients were managed in dedicated thoracic surgery wards. For resecting benign lesions, 56 lobectomies, 36 wedge, and two pneumonectomies were performed. For malignant lesions, 555 lobectomies, 93 wedge/segmentectomies, and 130 pneumonectomies were performed. Seventeen sleeve lobectomies were performed and included in the analysis.

Postoperative treatment was standard in both units and focused on early mobilization, chest physiotherapy, thoracotomy pain control, antibiotic, and anti-thrombotic prophylaxis. Postoperative chest pain was controlled by means of epidural or continuous intravenous analgesia, which was titrated to keep the pain visual score below 4 (in a scale ranging from 0 to 10) during the first postoperative 48—72 h (pain score was assessed twice daily, during morning and afternoon rounds).

Operability was evaluated by means of pulmonary function tests, blood gas analysis, electrocardiogram, echocardiography, cardiopulmonary exercise testing, and more invasive cardiologic procedure if needed.

Criteria for inoperability were a predicted postoperative FEV1 (ppoFEV1) $< 30\%$ in association with a poor exercise capacity (height at stair climbing test lower than 12 m or VO2max < 10 ml/(min kg)), or cardiac instability. All patients with a concomitant cardiac disease were judged hemodynamically stable at the time of operation. Whenever technically feasible and oncologically appropriate, those patients with prohibitive cardiorespiratory function underwent wedge resection or segmentectomy.

This is a retrospective analysis performed on prospectively compiled, computerized, quality-controlled databases.

Pulmonary function tests were performed according to the American Thoracic Society criteria and results of spirometry were collected after bronchodilator administration.

Carbon monoxide lung diffusion capacity was measured by the single breath method. FEV1 and DLCO values were expressed as percentage of predicted for age, sex and height, according to the European Community for Steel and Coal prediction equations [14].

Postoperative complications and mortality were considered as those occurring within 30 days postoperatively, or over a longer period if the patient was still in the hospital.

According to previous studies [5,15] and for the sake of comparison, the following complications were included: respiratory failure requiring mechanical ventilation for more than 48 h; pneumonia (fever $> 38\ ^{\circ}$C, abnormal findings on chest radiograph, increased white blood cell count); atelectasis requiring bronchoscopy; adult respiratory distress syndrome (ARDS); pulmonary edema (as defined by clinical and radiographic findings); pulmonary embolism; myocardial infarction; hemodynamically unstable arrhythmia requiring medical treatment and prolonged hospital stay; cardiac failure.

For the purpose of the present study, a concomitant cardiac disease (cardiac co-morbidity) was defined as follows: previous cardiac surgery, previous myocardial infarction, history of coronary artery disease, current treatment for hypertension, arrhythmia, or cardiac failure.

2.1. Statistical analysis

Correlation coefficients between FEV1 and DLCO were obtained in the entire dataset and in different subsets of patients stratified by age (older or younger than 70 years), gender, cause of operation (benign vs malignant), presence of cardiac disease and airflow limitation (FEV1 $< 80\%$). In patients with a FEV1 $> 80\%$, a number of variables were tested for a possible association with postoperative complications by means of the unpaired Student's *t*-test or Mann—Whitney test (continuous variables) and the chi-square test (categorical variables). The Shapiro—Wilk normality test was used to assess the normal distribution of the continuous variables. The following variables were initially screened by univariate comparison: age, gender, type of operation (wedge/lobectomy/pneumonectomy), body mass index (BMI, kg/m^2), type of disease (benign vs malignant), cardiac co-morbidity, neoadjuvant chemotherapy, FEV1, DLCO, predicted postoperative FEV1 (ppoFEV1), predicted postoperative DLCO (ppoDLCO), ppoFEV1 $< 40\%$, and ppoDLCO $< 40\%$. Predicted postoperative lung functions (ppoFEV1 and ppoDLCO) were calculated by the formula: ((preoperative lung function/number of preoperative functioning segments) $\times$ number of postoperative functioning segments). The number of functioning segments was estimated by means of CT scan, bronchoscopy, and quantitative perfusion lung scan. ppoFEV1 and ppoDLCO were expressed either as continuous variables or as categorical ones, choosing the high-risk cut-off value of 40% [5]. All variables were complete.

Variables with a $p < 0.10$ in the univariate analysis were used as independent variables in a stepwise logistic regression analysis (dependent variable: presence of cardiopulmonary complications). To avoid multicolinearity, only one variable in a set of variables with a correlation coefficient greater than 0.5 was selected by bootstrap analysis and used as independent variable in the regression analysis. The regression analysis was in turn validated by bootstrap analysis. In the bootstrap procedure, 1000 samples of 508 observations (the same number of observations as the original database of patients with FEV1 $> 80\%$) were selected with replacement from the original set observations. For each sample, stepwise logistic regression was performed entering the variables with $p < 0.1$ in univariate analysis. The stability of the final stepwise model can be assessed by identifying the variables that enter most frequently in the repeated bootstrap models and comparing those variables with the variables in the final stepwise model. If the final stepwise model variables occur in a majority (>50%) of the bootstrap models, the original final stepwise regression model can be judged to be stable.

All tests were two-tailed, with a significance level of 0.05, and were performed on the statistical softwares Statview 5.0 (SAS Inc., Cary, NC, USA) and STATA 8.2 (Stata Corp., College Station, TX, USA).

3. Results

Table 1 shows the characteristics of the patients in the study.

Table 2 shows the correlation coefficients between FEV1 and DLCO in the entire dataset and in different subsets of patients. In all cases, the correlation coefficients were lower than 0.5.

In patients with FEV1 greater than 80% (508 cases, 58% of the entire dataset), 219 (43%) had DLCO < 80%, 124 (24%) had DLCO < 70%, 46 (9%) had DLCO < 60%, and 35 (7%) had ppoDLCO < 40%. In these latter patients, morbidity and mortality rates were higher than in those with ppoDLCO ≥ 40% 40% (37% vs 17.5%, $p = 0.004$; 8.6% vs 3%, Fisher's exact test, $p = 0.10$, respectively).

Ninety-seven patients with FEV1 > 80% (19%) experienced cardiopulmonary complications, 17 of whom died (3.3% mortality rate). Table 3 shows the predictors of cardiopulmonary morbidity in patients with FEV1 greater than 80%. After logistic regression analysis, age ($p = 0.007$) and ppoDLCO < 40% ($p = 0.004$) were the only significant and reliable predictors of morbidity.

4. Discussion

In most thoracic surgery units, DLCO is not routinely measured in all lung resection candidates but only in those patients with impaired FEV1 [11—13]. This selective attitude is based on the assumption that a subject with a normal FEV1 very unlikely will have a compromised gas exchange.

However, as FEV1 and DLCO measure two completely different aspects of the pulmonary function (airflow and gas exchange), which may show in turn different degrees and trends of deterioration, we hypothesized that these two parameters would not necessarily be highly correlated between each other. Therefore, the objective of the present analysis was to assess the degree of correlation between FEV1 and DLCO in candidates for lung resection from two centers that measure them systematically before operation.

Table 1
Characteristics of the patients in the study (872 patients)

Variables	
Age (years)	65.5 ± 10.7
Elderly, >70 years old, *n* (%)	330 (38%)
BMI (kg/m^2)	25.9 ± 4.4
FEV1%	84.5 ± 19.4
DLCO%	77.8 ± 19.5
ppoFEV1%	67.1 ± 18.2
ppoDLCO%	61.9 ± 18
Cardiac co-morbidity, *n* (%)	338 (39%)
Neoadjuvant chemotherapy, *n* (%)	93 (11%)

Results are presented as means ± standard deviations unless otherwise specified. BMI: body mass index.

Table 2
Correlation between FEV1 and DLCO in the entire dataset and in different subsets of patients in the study

Groups	Number of patients	FEV1—DLCO correlation coefficients
Entire dataset	872	0.38
Elderly (>70 years old)	330	0.38
Young (≤70 years old)	542	0.39
FEV1 > 80%	508	0.20
FEV1 ≤ 80%	364	0.23
ppoFEV1 < 40%	50	0.19
ppoFEV1 ≥ 40%	822	0.35
Males	639	0.37
Females	233	0.49
Benign disease	94	0.5
Malignant disease	778	0.37

We found a modest correlation between FEV1 and DLCO in our patients, even when the analysis was stratified by age, gender, cause of operation (benign vs malignant), presence of cardiac disease, and airflow limitation. Moreover, a substantial number of patients without airflow limitation (more than 40%) had an impaired lung diffusion capacity, and 7% of them had a critical ppoDLCO value (ppoDLCO < 40%). These patients experienced morbidity and mortality rates twofold and almost threefold higher than in those with ppoDLCO ≥ 40%, respectively. Furthermore, after controlling the effect of other factors with logistic regression analysis, ppoDLCO < 40% was an independent predictor of complications in patients without airflow limitation.

Our results show that, even in subjects with otherwise apparently normal pulmonary function, diffusion capacity has a role in predicting postoperative morbidity, confirming previous studies, which, however, did not analyze this subset of patients separately [1—10].

The modest correlation between FEV1 and DLCO and the capacity of ppoDLCO to discriminate between patients with

Table 3
Predictors of postoperative cardiopulmonary morbidity in patients with FEV1 > 80% (508 cases)

Variables	Estimates	SE	Odds ratio	95% CI	*p*-value	Bootstrap frequency (%)
Intercept	−3.6					
Age	0.03	0.01	1.03	1.01—1.05	0.007	77
ppoDLCO < 40%	1.1	0.4	3	1.4—6.3	0.004	81

Parsimonious model. Hosmer—Lemeshow statistics 9.6, $p = 0.3$; *c*-index 0.65. Bootstrap frequency: frequency of significancy in 1000 bootstrap samples.

and without complications in subjects with a normal FEV1 do not warrant the approach to confine DLCO measurement only to patients with a FEV1 $< 80\%$.

A possible limitation of this study may be its retrospective and multicentric nature, which could have determined possible variations in variables' definition and recording. However, after careful scrutiny of the postoperative management policy in each unit, the authors considered the data selected and used in the analysis as reliable and consistent across the two centers. Moreover, the principal investigators of the study (A.B. and G.R.) are part of the European Thoracic Database Committee and share the same methods and purposes in variables definition and database quality control.

In conclusion, in view of the results of this analysis, we recommend to measure DLCO routinely in all candidates for lung resection, irrespective of their FEV1 value, in order to improve surgical risk stratification. It is the hope of the authors that the widespread measurement of DLCO may allow the inclusion of this variable as a predictor to further refine future risk models developed from the European Thoracic Surgery database [11].

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