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CHRONOTROPIC INCOMPETENCE PREDICTS MORTALITY IN SEVERE OBSTRUCTIVE PULMONARY DISEASE

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Abstract

We evaluated the prevalence of chronotropic incompetence (CI), a marker of autonomic dysfunction, and its prognostic value in patients with chronic obstructive pulmonary disease (COPD). We performed a retrospective analysis of 449 patients with severe COPD who underwent a cardiopulmonary exercise test, after excluding patients with lung volume reduction surgery, left ventricular dysfunction and those not in sinus rhythm. CI was defined as percent predicted heart rate reserve (%HRR). Events were defined as death or lung transplant during a median follow-up of 68 months. Median age was 61 years; median percent predicted forced expiratory volume in one second (%FEV_1) of 25% and median %HRR of 33%. The hazard ratio for an event in the lowest quartile of %HRR, taking the highest quartile as reference, was of 3.2 (95% Confidence Interval: 2.1–4.8; $p<0.001$). In a multivariate regression model, %HRR was an independent predictor of events. In conclusion, CI was an independent and powerful outcome predictor in patients with severe COPD.

Keywords

Chronic obstructive pulmonary disease; Chronotropic incompetence; Heart rate reserve

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1. Introduction

The prevalence of Chronic Obstructive Pulmonary Disease (COPD) as a health problem is increasing (Celli, 2010; Celli and MacNee, 2004) and chronic lower respiratory diseases is the third leading cause of death in the United States (Miniño et al, 2010). Currently, forced expiratory volume in 1 second (FEV_1) is seen by many to be the best predictor of mortality in COPD (Celli and MacNee, 2004). However, FEV_1 does not fully express the complexity of COPD (Celli, 2010), and other measures may have a role in evaluating mortality risk such as long term oxygen therapy, body mass index (BMI), the Manchester Respiratory Activities of Daily Living Questionnaire score (Yohannes et al, 2002) as well as age, exercise capacity, emphysema distribution (Martinez et al, 2006) and 6-minute walk distance (Pinto-Plata et al 2004). Although airflow limitation is the defining characteristic of COPD, the risk for all cardiovascular diseases is higher in COPD patients than in age and gender matched controls (Curkendall et al, 2006) and current models for risk assessment such as the BODE index (Celli et al, 2004) do not include heart related parameters.

Chronotropic Incompetence (CI) is defined as the inability of the heart to increase its rate commensurate with increased activity or demand and it has been established as a predictor of cardiovascular events and all-cause mortality (Jae et al, 2006; Lauer et al, 1999, 1998). It can be easily measured in a maximal exercise test and is defined as a failure to achieve 85% of the age-predicted maximum heart rate, a heart rate reserve (HRR) < 80% or a chronotropic response index < 0.80 (Brubaker et al, 2011). The mechanism of CI in other chronic diseases, such as heart failure, is thought to be secondary to chronic overactivation of the sympathetic system and subsequent downregulation of cardiac β-adrenoreceptor densities (Colucci et al, 1989). In heart failure, CI is associated with decreased exercise capacity (Jorde et al, 2008). Patients with COPD also have marked sympathetic activation and depressed heart rate variability (Andreas et al, 2005; Bartels et al, 2000). To our knowledge, no one has examined the role of CI as a prognostic factor in patients with COPD. Our hypothesis was that patients with severe COPD would have altered CI, which is associated with increased mortality.

2. Material and methods

A retrospective chart review was performed on all COPD patients diagnosed according to standard criteria (Celli and MacNee, 2004), who had cardiopulmonary exercise testing (CPET) in the past 10 years at Columbia University Medical Center. The study was approved by the Institutional Review Board of our center (IRB#AAAF3710). All patients were referred for exercise tests as part of their standard clinical evaluation. We excluded patients who did not have a pulmonary function test (PFT) performed at our institution, those who had an FEV_1 of >50%, and subjects who underwent lung volume reduction surgery during follow-up, as this could be a confounder in the survival analysis. We also excluded patients who were not in sinus rhythm or had a left ventricular ejection fraction <45%, as well as those in whom an echocardiogram had not been obtained within one year prior to study inclusion. None was on beta blockade at the time of testing. Events during follow-up were defined as death or lung transplantation from the date of CPET until August

2010. Mortality data were obtained via the Social Security Index and the date of lung transplantation was determined by chart review.

2.1. Cardiopulmonary Exercise Testing

CPETs were performed on an electronically braked cycle ergometer. All tests were performed on 30% supplemental oxygen. Each patient's CPET ramping protocol was determined by their maximal voluntary ventilation (MVV) test. Those who achieved 40 L/min or less on the MVV performed a 5-watt per minute ramping protocol, while those with more than 40 L/min performed a 10-watt ramping protocol (Fishman et al, 2003). All patients took an inhaled short acting beta agonist between 20 minutes and 2 hours before testing. The protocol consisted of a 5 minute resting baseline data collection, followed by a warm-up of 3 minutes of unloaded pedaling. Patients maintained a cadence between 50–60 revolutions per minute (RPM) for the duration of the test. If at any time they dropped their cadence below 40 RPM and remained below 40 RPM for 5 seconds, the test was terminated. Patients exercised to their peak capacity according to the American Thoracic Society (ATS) standard test end criteria (ATS/ACCP, 2003). CPET variables recorded were blood pressure, heart rate (HR), peak watts attained, peak oxygen consumption (VO_2), respiratory exchange ratio, minute ventilation, rate of carbon dioxide production (VCO_2) and respiratory rate. All percent of predicted exercise parameters were calculated using formulas by Wasserman et al (Wasserman et al, 1999). To assess CI, we used the percentage of heart rate reserve achieved (%HRR), defined as: (peak HR−rest HR)/(Age predicted peak HR−rest HR) × 100, as this marker has been shown to be superior to the percentage of maximal age predicted heart rate to predict cardiac death (Azarbal et al, 2004). Age predicted peak HR was calculated using Tanaka's formula: 208–0.7 x age (Tanaka et al, 2001).

2.2. Pulmonary function testing

All PFT's were performed according to ATS criteria (Wanger et al, 2005) and included forced vital capacity (FVC) and FEV_1 in all patients and total lung capacity (TLC), residual volume (RV) and single breath diffusion capacity of the lung for carbon monoxide (DLCO) in 79% of patients. Percent predicted FEV1 (%FEV_1) (Crapo et al, 1981), percent predicted DLCO (%DLCO) (Crapo and Morris, 1981), percent predicted forced vital capacity (%FVC) (Crapo et al, 1981), percent predicted residual volume (%RV) and percent predicted total lung capacity (%TLC) (Crapo et al, 1982) were calculated as described in prior papers.

2.3. Statistical analysis

Continuous variables were explored for normal distribution according to histograms and the Kolmogorov-Smirnov test. Variables that follow a normal distribution were expressed as mean ± standard deviation and those that did not were expressed as median and interquartile range (IQR). The study cohort was divided into quartiles based on the %HRR, with the lowest quartile representing the greatest degree of CI. Comparisons between quartiles were performed with the Anova linear trend test for variables with a normal distribution and with the Jonckheere-Terpstra test for variables that did not follow a normal distribution. Categorical variables are presented as number and percentage and are compared using the linear trend test.

For survival analysis we considered death or lung transplant as an event. In order to illustrate the effect of %HRR on event-free survival rates, Kaplan-Meier curves for cumulative survival were constructed for patients in the different quartiles of %HRR. Differences in event-free survival rates were tested using the Cox-Mantel log-rank test. The comparison of hazard ratios between patients in the different quartiles of %HRR, taking the highest quartile as reference, was performed using the Mantel-Haenszel test for trend.

The associations between analyzed variables and survival were established using univariate Cox proportional hazards analyses. We then performed backward step multivariate Cox proportional hazard analysis with an inclusion criteria of $p<0.05$ and an exclusion criteria of $p>0.10$. In the first model we included age, gender and all the variables that were significant in the univariate analysis: BMI, %HRR, percent predicted peak VO_2 (as a measure of exercise capacity), peak respiratory exchange ratio, peak minute ventilation, the ratio of minute ventilation to the rate of carbon dioxide production (VE/VCO_2), $\%FEV_1$, %FVC, %TLC, %RV and %DLCO. However this analysis was limited by the fact that 21% of patients did not have measures of %TLC, %DLCO or %RV, so we then used a second model including all the above variables except for these three. The assumptions of the proportional hazard were tested for all the covariates. Correlations were analyzed by the Pearson correlation coefficient. All statistical tests were performed using SPSS version 18 (SPSS, Chicago, IL). All tests were two-sided. A value of $p<0.05$ was considered statistically significant.

3. Results

3.1. Patient cohort

We performed CPET in 926 COPD patients from November 2000 to June 2010. We excluded 55 patients who underwent lung volume reduction surgery. Of the 871 patients left, 342 (39%) patients had either died or undergone lung transplantation during follow-up. We further excluded 70 patients who did not have PFTs done at our center and 121 who had FEV_1 >50%. We also excluded 14 patients who were not in sinus rhythm, 200 with no echocardiogram and 17 with a left ventricular ejection fraction below 45%. We were left with 449 patients whose baseline characteristics and PFT parameters are shown in table 1. This cohort had 188 (41%) events, 117 deaths and 71 lung transplantations, during a median follow-up time of 68 (IQR: 34–144) months. The event rate was 5.3 per 100 persons-year.

3.2. Cardiopulmonary exercise test

Results of CPET are shown in table 2 and mean %HRR was 34 ± 16%, indicating severe CI. When we stratified the patients into quartiles according to the %HRR (table 3) we found that the %HRR was associated with increased pulmonary obstruction, TLC and RV along with decreased DLCO but not with age, sex or BMI. As expected, %HRR was positively associated with peak exercise capacity and peak minute ventilation and inversely with the VE/VCO_2 ratio.

3.3 Predictors of events

The hazard ratio for an event according to the %HRR and taking the highest quartile as reference was of 3.2 (95% Confidence interval: 2.1–4.8) for the lowest quartile, of 2.3 (95% Confidence Interval: 1.5–3.5) for the second quartile and of 1.7 (95% Confidence Interval: 1.1–2.6) for the third quartile. Mantel-Haenszel test for trend showed a $p<0.001$. Figure 1 shows how the survival curves are markedly different according to the different quartiles of %HRR. The univariate analysis for all the variables to predict an event can be seen in table 4. All variables were significant with the exception of age and gender. The results of the first multivariate analysis are shown in table 5. The only significant predictors of death and lung transplant were the %HRR, $\%FEV_1$, percent-predicted peak VO_2 and %DLCO. Table 6 shows that if the %TLC, %DLCO and %RV are not included in the second model of the multivariate analysis, the only significant predictors of events are %HRR, $\%FEV_1$ and VE/VCO_2. When performing this same analysis only for all cause mortality, censored for lung transplant, %HRR also came up as a significant predictor of mortality (Hazard Ratio = 0.980; $p = 0.004$) alongside $\%FEV_1$ (Hazard Ratio = 0.947; $p<0.001$), Age (Hazard Ratio = 1.046; $p = 0.001$) and VE/VCO_2 (Hazard Ratio = 1.041; $p = 0.001$). The correlation between $\%FEV_1$ and VE/VCO_2 with the %HRR showed an R of 0.275 and −0.226 respectively.

4. Discussion

After examining the role of CI as a prognostic tool in patients with severe COPD, our main finding is that CI is extremely prevalent and an independent predictor of death or the need for lung transplantation in this population.

4.1. Chronotropic incompetence and COPD

We found that almost all patients in our cohort had significant CI. In our study we did not use the Wilkoff model because many of our patients had poor exercise capacity and in most studies the inability of reaching stage 2 in a standard bruce protocol precludes using this measure of CI (Lauer et al, 1996). The cause of CI in COPD may be due to a number of factors, including a significant history of smoking (Lauer et al, 1997), ventilatory limitation to exercise (O'Donnell, 2008), the presence of subclinical atherosclerosis and cardiovascular disease (Curkendall et al, 2006; Soriano et al, 2005) and the profound neurohormonal activation that occurs in patients with COPD secondary to hypoxemia (Andreas et al, 2005). COPD patients also have increased plasma norepinephrine concentrations and myocardial norepinephrine turnover (Skamaki et al, 1999), as well as activation of the renin-angiotensin system (Stewart et al, 1994). In order to avoid confounding our results with alterations of CI from heart failure, we excluded any patient that could have left ventricular dysfunction and found that CI in COPD was inversely correlated with peak exercise capacity and with VE/VCO_2. In patients with chronic heart failure an increased VE/VCO_2 is also associated with impaired heart rate variability (Ponikowski et al, 1998). We also found that the CI was associated with increased pulmonary obstruction, TLC, RV and decreased DLCO, suggesting that CI is indeed linked to the severity of lung disease.

Dynamic hyperinflation disproportionate to the FEV_1, intrinsic positive end-expiratory pressure and pulmonary vascular hypertension may all contribute to CI and in a recent study

by our group we have demonstrated that if you can improve pulmonary function and decrease hyperinflation, such as that achieved after LVRS, CI improves (Armstrong et al, 2012).

Our findings are similar to those by Seshadri et al. who showed that CI and abnormal heart rate recovery after exercise is reflective of altered parasympathetic tone in patients with COPD. They found that $\%FEV_1$, impaired functional capacity, male gender and age predicted CI (Seshadri et al, 2004). Similarly, we have previously shown that patients with COPD have a reduced heart rate variability during maximal volitional exercise (Bartels et al, 2003). A recent study in patients without structural heart disease showed that individuals with CI have an altered heart rate variability in its low-frequency component after exercise and the ratio of low to high frequency component was also higher after exercise (Kawasaki et al, 2010). This suggests that CI was caused by sympathetic activation not translated into heart rate increase. The authors speculate that this might be caused by post-synaptic desensitization of the beta-adrenergic pathway in the sino-atrial node secondary to frequent sympathetic activation and this pathophysiology would be plausible in patients with COPD.

4.2. Increased mortality in patients with COPD and CI

While respiratory illness is the leading cause of mortality for patients with severe COPD, it is closely followed by cardiovascular disease and cancer (Calverley et al, 2007). In our patients we looked at predictors of all-cause death and lung transplantation as a death equivalent. In the 2 multivariate models that we used, CI came out as an independent predictor of events. In the first model that included BMI, sex, age and all the variables from the CPET and PFT, the other predictors of events were DLCO, FEV_1 and peak VO_2. Exercise capacity and FEV_1 are well known predictors of mortality in COPD (Celli, 2010; Cote et al, 2007). DLCO on the other hand, has low reproducibility and has not been clearly associated with a worse prognosis, although a low DLCO correlates with the degree of emphysema in patients with COPD (Cote et al, 2007). In the National Emphysema Treatment Trial study, DLCO was strongly predictive of mortality in univariate models but its impact weakened in multivariate modeling (Martinez et al, 2006). Because TLC, DLCO or RV were missing in 21% of patients and these parameters are not easily accessible in the community, we used a second model that only included variables from a simple PFT (FEV_1 and FVC) and from the CPET, as well as BMI, sex and age. In this model the %HRR, $\%FEV_1$ and VE/VCO_2 were independent predictors of events (death and lung transplantation), but also of all cause mortality. To demonstrate that the %HRR was not a only a marker of increased obstruction we showed that the correlation between %HRR and %FEV1 is not sufficiently high to imply a problem of co-linearity. This is interesting, as an abnormal VE/VCO_2 response has been previously seen in patients with COPD and pulmonary hypertension (Holverda et al, 2008) and is thought to be a reflection of systemic disease severity.

To our knowledge, this is the first study that has shown CI to be an independent predictor of adverse events in a COPD population. Whether the presence and severity of CI is a reflection of advanced systemic pulmonary disease with associated increased sympathetic nervous system activation is currently unknown. However, the ARIC study showed that a

low FEV1 and an obstructive respiratory disease were strongly and independently associated with the risk of incident HF (Agarwal et al, 2012) and a recent study has shown that β-blockers may reduce mortality and risk of exacerbations in patients with COPD (Rutten et al, 2010), suggesting that reversing sympathetic activation may be important. Given that better risk assessment tools are needed, especially in the more severe COPD population, where timing of lung transplantation is critical, we think that consideration should be given to the inclusion of CI in a modified prospective score, such as the BODE index, to better assess risk in patients with COPD.

4.3. Limitations

This is a retrospective study of patients referred for CPET at a single institution and as such there may be a selection bias of referral. Also, we did not have complete PFT and echocardiographic data in all patients and this reduced the size of the sample analyzed. However the event rate during follow-up of the 871 patients that did not undergo lung volume reduction surgery was of 39%, very similar to the 41% event rate in the cohort that was analyzed.

Although we excluded patients with left ventricular systolic dysfunction and those that were not in sinus rhythm, we did not evaluate the presence of previous cardiovascular disease, the presence of diastolic heart failure and detailed smoking history; all of which are associated with CI (Lauer et al, 1998; Lauer et al, 1997; Phan et al, 2010). Additionally, we do not have data on bronchodilators, theophylline or other medications that may affect heart rate, although it is likely that all the patients were on beta agonists.

5. Conclusions

We have shown that CI, measured by %HRR, is highly prevalent in a cohort of patients with severe COPD and is a strong independent predictor of mortality or lung transplantation. Adding the evaluation of CI, an easily determined variable, to other pulmonary function parameters or to a standard tool such as the BODE index may improve the prognostic assessment of patients with severe COPD.

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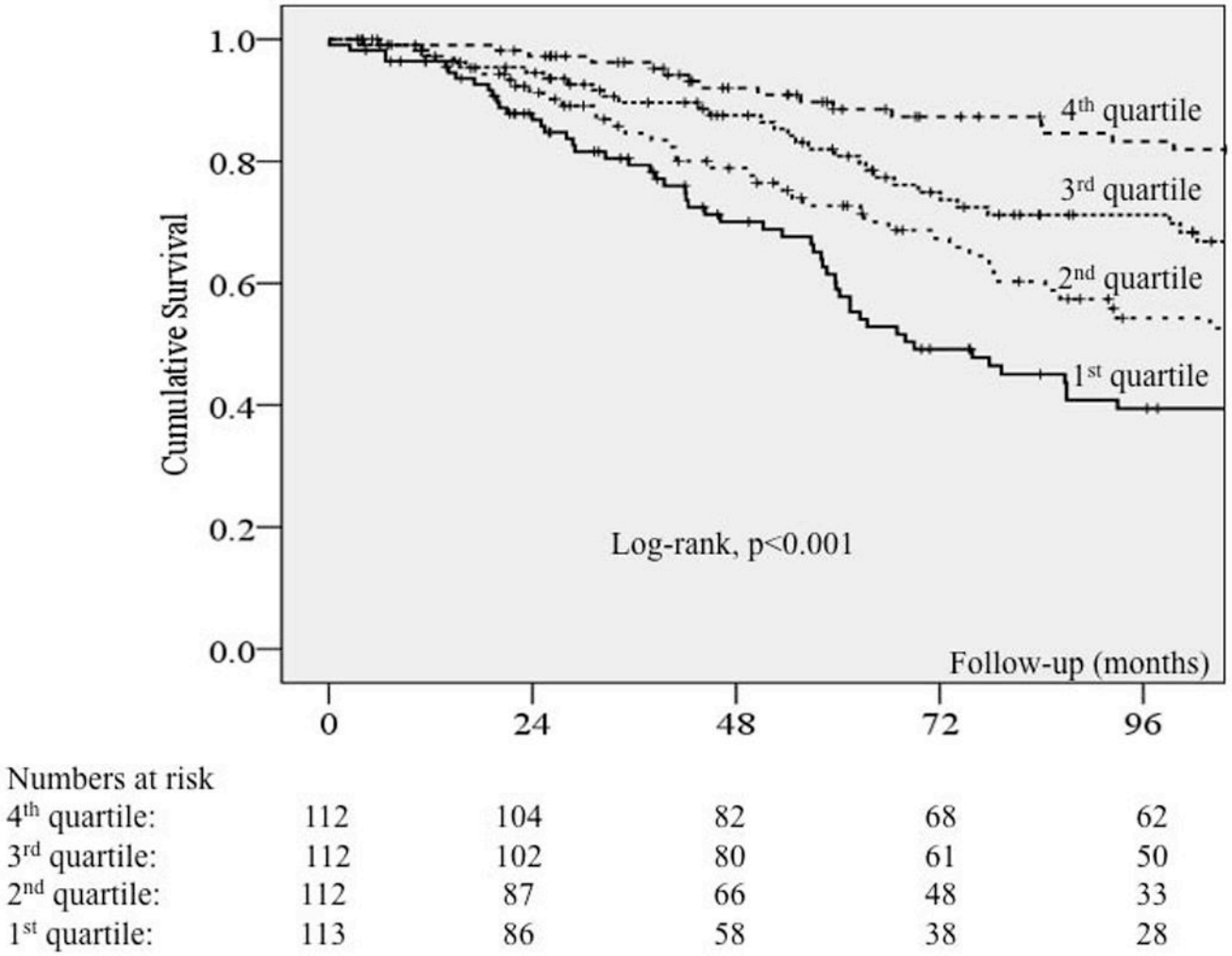
Highlights

- Patients with chronic obstructive pulmonary disease performed a cardiopulmonary exercise test.
- Retrospective follow-up for adverse events: death and lung transplant.
- Chronotropic incompetence was highly prevalent in this cohort.
- Chronotropic incompetence was an independent predictor of adverse events.



Numbers at risk					
4th quartile:	112	104	82	68	62
3rd quartile:	112	102	80	61	50
2nd quartile:	112	87	66	48	33
1st quartile:	113	86	58	38	28

Figure 1. Survival according to Heart Rate Reserve

Cumulative survival in patients with severe chronic pulmonary obstructive disease divided in quartiles according to the percentage of heart rate reserve achieved during a cardiopulmonary exercise test.

Table 1

Baseline characteristics and pulmonary function parameters.

Variable	N=449
Age (years)	61 (56–66)
Male gender	213 (47)
Body mass index (kg/m^2)	24.5 (21.5–27.8)
FEV_1 (% predicted)	25 (19–33)
FVC (% predicted)	55 (45–69)
FEV_1/FVC ratio (%)	35 (30–42)
DLCO (% predicted)	29 (23–39)
TLC (% predicted)	116 (103–127)
RV (% predicted)	208 ± 70

Quantitative variables that are normally distributed are expressed as mean ± standard deviation. Quantitative variables that are not normally distributed are expressed as median (interquartile range). Categorical variables are expressed as a number (percentage). FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; DLCO: Diffusion capacity of the lung for carbon monoxide; TLC: Total lung capacity; RV: Residual volume.

Table 2

Cardiopulmonary exercise test parameters.

Variable	N=449
Resting Heart Rate (bpm)	91 ± 15
Peak Heart Rate (bpm)	116 ± 15
Heart Rate Reserve (%)	34 ± 16
Peak Watts (% predicted)	22.6 (13–36)
Peak oxygen consumption (% predicted)	41 (31–51)
Peak Respiratory Exchange Ratio	0.86 (0.79–0.96)
Peak minute ventilation (L/min)	23.5 (17.8–32.1)
Peak VE/VCO_2	35.5 (31–40)

Quantitative variables that are normally distributed are expressed as mean ± standard deviation. Quantitative variables that are not normally distributed are expressed as median (interquartile range). VE/VCO_2: Ratio of minute ventilation to the rate of carbon dioxide production.

Table 3

Variables according to the quartiles of the percent heart rate reserve.

Variable	HRR<23% (N=113)	HRR 23–33% (N=112)	HRR 33–44% (N=112)	HRR>44% (N=112)	P value
Age (years)	61 (56–66)	61 (55–65)	62 (57–69)	61 (56–66)	0.522
Male gender	52 (46)	60 (54)	52 (46)	49 (44)	0.487
BMI (kg/m^2)	23.6 (21–27)	24.8 (22–28)	25.0 (23–29)	24.6 (22–27)	0.105
Peak VO_2 (% pred)	31 (24–40)	40 (29–47)	44 (36–53)	51 (40–60)	<0.001
Peak RER	0.82 (0.75–0.91)	0.85 (0.78–0.91)	0.88 (0.80–0.97)	0.90 (0.82–1.01)	<0.001
Peak VE (L/min)	18.2 (14–24)	23.4 (18–29)	25.0 (20–34)	27.4 (22–37)	<0.001
Peak VE/VCO_2	37.7 (32–43)	36.5 (32–40)	35 (30–39)	32 (29–38)	<0.001
FEV_1 (% pred)	20.5 (15–27)	22.4 (17–29)	26.6 (20–36)	28.2 (23–39)	<0.001
FVC (% pred)	46 (39–58)	52 (45–67)	57 (46–70)	61 (49–72)	<0.001
DLCO (% pred)	26 (20–36)	29 (21–38)	31 (25–43)	32 (26–39)	0.001
TLC (% pred)	122 (110–134)	117 (105–130)	113 (103–125)	111 (99–122)	<0.001
RV (% pred)	243 ± 76	216 ± 70	193 ± 55	180 ± 62	<0.001

Normally distributed variables are expressed as mean ± standard deviation and non-normally distributed variables are expressed as median (interquartile range). Categorical variables are expressed as a number (percentage). % pred: % predicted; HRR: Heart rate reserve; BMI: Body mass index; HR: Heart rate; VO_2: Oxygen consumption; RER: Respiratory exchange ratio; VE: Minute ventilation; VE/VCO_2: Ratio of minute ventilation to the rate of carbon dioxide production; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; DLCO: Diffusion capacity of the lung for carbon monoxide; TLC: Total lung capacity; RV: Residual volume.

Table 4

Predictors of death or lung transplant in patients with COPD. Univariate analysis.

Variable	Hazard Ratio	95% Confidence Interval	P value
Age (1 year)	0.988	0.982–1.014	0.813
Male gender	1.054	0.791–1.405	0.720
BMI, 1 kg/m^2	0.938	0.908–0.970	<0.001
HRR (1 %)	0.972	0964–0.981	<0.001
Peak VO_2 (1 % predicted)	0.962	0.951–0.973	<0.001
Peak RER (0.01)	0.971	0.959–0.984	<0.001
Peak VE (1 L/min)	0.954	0.937–0.970	<0.001
Peak VE/VCO_2 (1)	1.029	1.012–1.045	0.001
FEV_1 (1 % predicted)	0.944	0.928–0.961	<0.001
FVC (1 % predicted)	0.971	0.962–0.981	<0.001
TLC (1 % predicted)	1.014	1.006–1.022	0.001
RV (1 % predicted)	1.007	1.005–1.009	<0.001
DLCO (1 % predicted)	0.963	0.948–0.977	<0.001

BMI: Body mass index; HRR: Heart rate reserve; VO_2: Oxygen consumption; RER: Respiratory exchange ratio; MVV: Maximal voluntary ventilation; VE: Minute ventilation; VE/VCO_2: Ratio of minute ventilation to the rate of carbon dioxide production; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; DLCO: Diffusion capacity of the lung for carbon monoxide; TLC: Total lung capacity; RV: Residual volume.

Table 5

Significant predictors of death or lung transplant in patients with COPD. Model 1 of the multivariate analysis.

Variables	Hazard Ratio	95% Confidence Interval	P value
Heart Rate Reserve (1 %)	0.985	0.973–0.997	0.015
FEV_1 (1 % predicted)	0.969	0.940–0.999	0.036
DLCO (1 % predicted)	0.976	0.962–0.990	<0.001
Peak VO_2 (1 % predicted)	0.980	0.962–0.999	0.034

FEV_1: Forced expiratory volume in one second; DLCO: Diffusion capacity of the lung for carbon monoxide; VO_2: Oxygen consumption.

Table 6

Significant predictors of death or lung transplant in patients with COPD. Model 2 of the multivariate analysis.

Variables	Hazard Ratio	95% Confidence Interval	P value
Heart Rate Reserve (1 %)	0.981	0.971–0.991	<0.001
FEV_1 (1 % predicted)	0.945	0.927–0.962	<0.001
VE/VCO_2 (1)	1.036	1.016–1.055	<0.001

FEV_1: Forced expiratory volume in one second; VE/VCO_2: Ratio of minute ventilation to the rate of carbon dioxide production.