Maximal Oxygen Uptake Cannot Be Estimated From Resting Lung Function and Submaximal Exercise in Patients With Chronic Obstructive Pulmonary Disease

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■ **BACKGROUND:** Maximal oxygen uptake ($\dot{V}O_{2max}$) obtained from incremental exercise testing is a useful indicator of limited exercise capacity. Several prediction equations have been developed to estimate $\dot{V}O_{2max}$ in patients with chronic obstructive pulmonary disease (COPD), but agreement studies between estimated and measured $\dot{V}O_{2max}$ are lacking. This study aims to assess agreement between the 6 estimated $\dot{V}O_{2max}$ equations and direct measures of $\dot{V}O_{2max}$ evaluated during maximal incremental exercise testing in male COPD patients.

■ **METHODS:** Patients with stable COPD, in accordance with GOLD guidelines, were included in the study. Agreement between $\dot{V}O_{2max}$ obtained during incremental exercise testing and $\dot{V}O_{2max}$ obtained from 6 prediction equations were studied. To estimate $\dot{V}O_{2max}$ from anthropometric prediction equations, lung function variables and submaximal exercise testing were used.

■ **RESULTS:** Of the 60 male patients in the study, 12 were GOLD stage II, 24 GOLD stage III, and 24 GOLD stage IV. Five prediction equations underestimated the value of $\dot{V}O_{2max}$ in relation to measured $\dot{V}O_{2max}$: equations 1, 2, 3, 4, and 6, by 14%, 66%, 42.2%, 35%, and 23.3%, respectively. Conversely, prediction equation 5 overestimated measured $\dot{V}O_{2max}$ by 76.9%. Agreement between all $\dot{V}O_{2max}$ prediction equations and measured $\dot{V}O_{2max}$ was poor. Discrepancy between $\dot{V}O_{2max}$ prediction equations and measured $\dot{V}O_{2max}$ varied from −0.857 to 0.736 L/min.

■ **CONCLUSIONS:** The use of lung function at rest and submaximal exercise testing is inaccurate for determining $\dot{V}O_{2max}$, which cannot be estimated by prediction equations in patients with stable COPD.

K E Y W O R D S

chronic obstructive pulmonary disease

exercise tests

pulmonary function tests

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Maximal oxygen uptake ($\dot{V}O_{2max}$) is an important determinant of cardiorespiratory fitness and aerobic performance. Cardiopulmonary exercise testing (CPET) is a unique tool to assess the limits and mechanisms of exercise tolerance.[1-3] Cardiopulmonary exercise testing is physiologically and clinically useful in the evaluation of patients with chronic obstructive pulmonary disease (COPD). Determining exercise capacity through incremental exercise testing in COPD is important for establishing exercise tolerance and limitations, evaluating aerobic capacity, and optimizing exercise intensity in candidates for pulmonary rehabilitation. However, expensive equipment and skilled personnel are required to evaluate maximal oxygen uptake ($\dot{V}O_{2max}$).[4] Consequently, alternative methods have been developed to estimate $\dot{V}O_{2max}$.

Several equations for estimating $\dot{V}O_{2max}$ in patients with COPD have been published.[5-7] Data have demonstrated good correlation between anthropometric characteristics, lung function at rest, and/or submaximal exercise and $\dot{V}O_{2max}$. Nevertheless, it remains to be confirmed whether predicted $\dot{V}O_{2max}$ can accurately reproduce the real value of directly measured $\dot{V}O_{2max}$ in COPD patients. Furthermore, in these studies, agreement analyses between direct measure of $\dot{V}O_{2max}$ and predicted $\dot{V}O_{2max}$ based on anthropometric characteristics at rest, lung function, and/or submaximal exercise testing have never been applied. The correlation coefficient measures the strength of a relation between 2 variables but is not appropriate for helping the physician make clinical decisions. However, measuring agreement between 2 methods allows quantification of the differences between observations and establishes the limits of agreement or bias. This provides an interval within which 95% of differences between measurements using the 2 methods are expected to be included. This study aimed to assess agreement between the 5 estimated $\dot{V}O_{2max}$ equations and direct measures of $\dot{V}O_{2max}$ evaluated during maximal incremental exercise testing in male COPD patients.

METHODS

Patients with stable COPD, in accordance with GOLD guidelines, receiving clinical treatment at a secondary hospital, were included in the study. At the time of assessment, all patients had been clinically stable for the previous 6 months. Inclusion criteria were as follows: (1) age < 75 years; (2) forced expiratory volume in the first second (FEV_1) 70% or less of reference values and relationship between FEV_1 and forced vital capacity (FVC), $FEV_1/FVC \leq 65\%$; (3) $Pa{O_2} > 55$ mm Hg at rest with no recommendation for prescribing home oxygen therapy; and (4) no other significant diseases that could prevent patient evaluation. Exclusion criteria were psychiatric disturbances, heart disease, or relevant bone or joint disease. The hospital ethics committee approved the study and all patients gave informed consent.

Study Design

This cross-sectional prospective observational study was designed to assess agreement between $\dot{V}O_{2max}$ obtained during incremental exercise testing and $\dot{V}O_{2max}$ obtained from prediction equations. Patients underwent 3 days of evaluation involving lung function and respiratory muscle strength on the first day; 6-minute walk tests (6MWT) on the second day; and maximal incremental exercise testing on the final day. Technicians collected data daily and were blind to the objective of the study. Conventional medical treatment for patients was established by a chest physician and included short- and long-action β_2 agonist, anticholinergic therapy, and corticoids.

Outcome Measures

Lung function

Pulmonary function. Lung function testing included FVC, FEV_1, FEV_1/FVC, and maximal voluntary ventilation using spirometry (Datospir 91, SibelMed, Barcelona, Spain). Lung volumes, inspiratory capacity, total lung capacity, and residual volume were determined using the helium dilution technique, and lung carbon monoxide diffusing capacity (D_LCO) was calculated with the single-breath method (PFL2450; SensorMedics; Yorba Linda, CA). Pulmonary function values were based on the best of 3 efforts. Method and reference values were those recommended by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).[8,9]

Respiratory pressure was measured under static conditions, with maximal inspiratory pressure (PI_{max}) at residual volume and maximal expiratory pressure (PE_{max}) at total lung capacity. Both measurements were recorded using a manometer (model 163, SibelMed, Barcelona, Spain) following the method and procedure described previously.[10] Arterial blood gases were measured at rest (pH, $Pa{O_2}$, $Pa{CO_2}$) using an ABL 500 device (Radiometer; Copenhagen, Denmark). Reference values were those recommended by the SEPAR.[11-13]

Six-Minute Walk Test

All patients performed one 6MWT, conducted along a flat hospital corridor (30 m).[14] Each individual was instructed and received standardized encouragement to walk from one end of the corridor to the other, trying to cover the greatest distance possible in 6 minutes.[15] Oxygen saturation ($Sp{O_2}$) and heart rate were measured continuously with a pulse oximeter (Pulsox 5, Konica-Minolta AVL, Diessenhofen, Switzerland). Dyspnea level was recorded on a modified Borg scale (0-10) at the beginning and end of every test.[16] Patients whose $Sp{O_2}$ fell less than 90% during the walk test were administered oxygen to prevent desaturation. Test results in meters were converted to feet to calculate equations 1, 2, 3, and 4.

Incremental Exercise Test

All patients underwent 1 maximal incremental exercise test, limited by symptoms, on a cycle ergometer

(Collins/CPX, Braintree, MA), with breath-by-breath monitoring of gas exchange ($\dot{V}O_2$ [L/min] and $\dot{V}CO_2$ [L/min]), minute ventilation ($\dot{V}E$), breathing frequency, and tidal volume.[17] Simultaneously, heart rate and arterial oxygen saturation were also measured. The test was initiated after 3 minutes of stable exercise gas exchange at rest, with the signal stabilized and patients sitting comfortably in the cycling position. Patients were instructed to use unloaded cycling for 2 minutes to obtain target pedaling frequency, at 60 revolutions per minute to familiarize themselves with cycling while breathing through a mouthpiece. Incremental loading (100 kilopond-meters per minute) was then applied with the technician instructing and encouraging the patient to reach the maximum tolerated level, in accordance with Jones' protocol.[17] Breathlessness was assessed during the tests with a modified Borg scale.[16]

Estimation of Maximal Oxygen Uptake

Six previously published prediction equations were used in agreement analyses. All of these were predicted using anthropometric characteristics, lung function variables, and submaximal exercise testing. The formulas used to estimate $\dot{V}O_{2max}$ in liters per minute are detailed in Table 1.

Lung function values were obtained as previously described, distance in meters was determined in a 6MWT, and work was calculated by multiplying the distance walked in kilometers by bodyweight in kilograms.[18] Results expressed in milliliter per minute were converted to liters per minute.

Data Analysis

To calculate sample size, with 90% reliability, we chose a previously published[19] standard deviation for $\dot{V}O_{2max}$ (L/min) of 0.366 L/min. We obtained a possible mean difference of 0.155 L/min between estimated $\dot{V}O_{2max}$ and direct measures of $\dot{V}O_{2max}$, with a significance alpha level of 0.01 and 2-tailed approximation.

The results of $\dot{V}O_{2max}$, determined by 6 equations, were compared with the direct measure of $\dot{V}O_{2max}$ through 1-way ANOVA with Bonferroni *post hoc* correction and significance level of $P < .0025$. Pearson correlations were performed between each result of the six equations and direct measure of $\dot{V}O_{2max}$. Agreements between direct measure of $\dot{V}O_{2max}$ and estimated $\dot{V}O_{2max}$ in 6 equations were evaluated using Bland–Altman plots.[20] The results of Bland-Altman plots were presented as bias ± SD of the bias. Bias was represented by the mean differences between $\dot{V}O_{2max}$ and estimated $\dot{V}O_{2max}$. Upper and lower limits of agreement, which represent SD, are conventionally defined as the 2.5 and 97.5 percentiles of the distribution of the differences. Data were analyzed using GraphPad Prism 5 (GraphPad Software Inc) software. [AQ2] The level of significance was set at $P < .05$ with a 2-tailed approach.

RESULTS

Sixty male patients were enrolled in the study. Clinical characteristics are shown in Table 2. Of the 60 COPD patients taking part in the study, 12 were GOLD stage II, 24 were GOLD stage III, and 24 were GOLD stage IV.[21] All subjects exhibited hyperinflation and mild impairment in diffusing capacity for carbon monoxide. Cycle exercise duration was 8.8 ± 2.3 minutes, measured $\dot{V}O_{2max}$ was 1.1 ± 0.3 L/min (0.6-1.9 L/min) and maximal ventilation minute was 39 ± 12 L/min (19-65 L/min). All results of baseline characteristics, lung function, and exercise tests are shown in Table 2.

Comparison of Direct and Estimated $\dot{V}O_{2max}$

Five of 6 $\dot{V}O_{2max}$ prediction equations (equations 2-6) showed significant mean differences in relation to measured $\dot{V}O_{2max}$, as analyzed by Bonferroni multiple comparison tests. The value of $\dot{V}O_{2max}$ prediction

Table 1 • Details of the Multivariate Model for Predicted $\dot{V}O_{2max}$

Authors	Prediction Equation
Cahalin et al[5]	$\dot{V}O_{2max} = 0.006 \times [\text{distance (ft)} + 7.38]$
Cahalin et al[5]	$\dot{V}O_{2max} = [0.006 \times \text{distance (ft)}] - [0.104 \times \text{age (years)}] + [0.052 \times \text{weight (kg)}] + 2.9$
Cahalin et al[5]	$\dot{V}O_{2max} = [0.006 \times \text{distance (ft)}] - [1.19 \times \text{FVC (L)}] + [1.95 \times FEV_1\ \text{(L)}] + 4.13$
Cahalin et al[5]	$\dot{V}O_{2max} = [0.005 \times \text{distance (ft)}] - [(0.162 \times \text{age (years)}] + [0.05 \times \text{weight (kg)}] - [2.04 \times \text{FVC (L)}] + [2.45 \times FEV_1\ \text{(L)}] + [0.084 \times D_LCO\ (\text{mL}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1})] + 9.75$
Carter et al[6]	$\dot{V}O_{2max} = 299.76 + [(0.013 \times \text{work (m kg)}] + [19.11 \times D_LCO\ (\text{mL}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1})] + [66.73 \times \text{FVC (L)}] + [-0.71 \times PI_{max}\ (cmH_2O)] + [2.55 \times \text{weight}] + [-4.44 \times \text{age})]$
Chuang et al[7]	$\dot{V}O_{2max} = 106 + [676 \times D_LCO\ (\%)] + [20 \times \text{work (m kg)}]$

Abbreviations: D_LCO, lung diffusion capacity of carbon monoxide; FEV_1, forced expiratory flow in the first second in liters; FVC, forced vital capacity in liters; PI_{max}, maximal inspiratory pressure; $\dot{V}O_{2max}$, maximal oxygen uptake.

Table 2 • Anthropometric Data, Lung Function, and Aerobic Capacity of Patients

	Total Group	GOLD II	GOLD III	GOLD IV
N	60	12	24	24
Age, y	65 ± 6	65 ± 6	65 ± 7	66 ± 7
Weight, kg	71 ± 10	75 ± 12	71 ± 10	69 ± 10
Height, cm	166 ± 6	168 ± 6	165 ± 6	166 ± 5
BMI, kg/m^2	26 ± 3	27 ± 4	26 ± 3	25 ± 3
FVC, L	2.7 ± 0.6	3.3 ± 0.3	2.7 ± 0.6	2.3 ± 0.6
FEV_1, L	1.1 ± 4.0	1.7 ± 0.2	1.15 ± 0.2	0.7 ± 0.14
FEV_1, %	34 ± 12	53 ± 3	37 ± 5	22 ± 4
FEV_1/FVC, %	40 ± 11	50 ± 7	43 ± 9	30 ± 5
TLC, L	6.5 ± 1	6.3 ± 0.7	6.4 ± 1.1	6.6 ±1
TLC, %	110 ± 16	105 ±14	109 ±16	112 ± 17
FRC, L	3.8 ± 0.9	3 ± 0.6	3.7 ± 0.9	4.3 ± 0.8
FRC, %	109 ± 16	136 ± 28	175 ± 43	199 ± 35
D_LCO, %	60 ± 27	84 ± 30	63 ± 19	45 ± 22
PI_{max}, cmH_2O	75 ± 20	90 ± 23	74 ± 19	67 ± 15
$\dot{V}O_{2max}$, L·min^{-1}	1.1 ± 0.3	1.4 ± 0.3	1.2 ± 0.2	0.9 ± 0.2
HR-rest, bpm	85 ± 15	87 ± 18	81 ± 13	87 ± 15
HR-max, bpm	126 ± 17	135 ± 18	127 ± 15	122 ± 18
6MWT, m	306 ± 58	332 ± 58	312 ± 55	284 ± 53
Work of walking, mkg	21 ± 5	25 ± 7	22 ± 5	19 ± 4

Abbreviations: bpm, beats per minute; BMI, body mass index; D_LCO, lung carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in the first second; FRC, functional residual capacity; FVC, forced vital capacity; HR-max, heart rate at maximal cardiopulmonary exercise test; HR-rest, heart rate at rest; 6MWT, 6-minute walking test; work of walking, calculated by multiplying the distance walked (m) by body weight (kg); TLC, total lung capacity; $\dot{V}O_{2max}$, maximal oxygen uptake.

equation 1 was not significantly different when compared to measured $\dot{V}O_{2max}$ (Figure 1). Five prediction equations underestimated the value of measured $\dot{V}O_{2max}$ (equations 1, 2, 3, 4, and 6, by 14%, 66%, 42.2%, 35%, and 23.3%, respectively). Conversely, $\dot{V}O_{2max}$ 5 prediction equation overestimated measured $\dot{V}O_{2max}$ by 76.9%.

The invalid test for each equation was calculated considering the minimum difference between measured and predicted $\dot{V}O_{2max}$, with a value of 0.155 L/min established by sample calculation. We found that in all 6 equations the invalid test varied between 68.3% and 98%. In addition, the coefficient of variation for each prediction equation was high when the previously recommended coefficient of variation of 2% to 4% was used. The mean and SD results for each equation are displayed in Table 3. All prediction equations were significantly correlated to measured $\dot{V}O_{2max}$ (r = 0.431 to r = 0.681, $P < .001$), as shown in Figure 2.

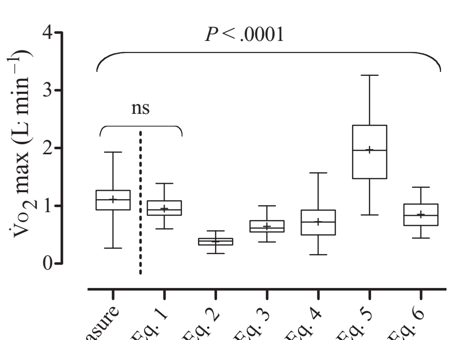

Figure 1. Results of direct maximal oxygen uptake ($\dot{V}O_{2max}$) measured and estimated by predicted equations.

Poor agreement was recorded between all $\dot{V}O_{2max}$ prediction equations and measured $\dot{V}O_{2max}$. Standard deviation of the bias in prediction equations was greater than the difference of 0.155 L/min established by sample calculation. Discrepancy between $\dot{V}O_{2max}$ prediction equations and measured $\dot{V}O_{2max}$ ranged from 0.857 to 0.736 L/min. The absence of agreement between $\dot{V}O_{2max}$ prediction equations and measured $\dot{V}O_{2max}$ is shown in Figure 3.

DISCUSSION

This study assessed the agreement between equations proposed to estimate $\dot{V}O_{2max}$ with a direct measure of $\dot{V}O_{2max}$ during maximal incremental exercise testing in male COPD patients. Poor agreement was found in all equations evaluated. The limit of agreement analysis revealed a wide variation among equations. Although mean differences (bias) between measured and estimated

Table 3 • Invalid Results of $\dot{V}O_{2max}$ When Applied to Predictive Equations in Patients With Chronic Obstructive Pulmonary Disease

Prediction Equation	$\dot{V}O_{2max}$, L·min^{-1}	CV, %	Invalid Tests Total (%)
Equation 1	0.952 ± 0.170	17.87	42 (70)
Equation 2	0.376 ± 0.086	22.98	59 (98)
Equation 3	0.644 ± 0.147	22.85	57 (95)
Equation 4	0.383 ± 0.182	47.66	59 (98)
Equation 5	1.970 ± 0.600	30.47	56 (93)
Equation 6	0.855 ± 0.238	27.87	44 (73)

Abbreviations: CV, coefficient of variation; $\dot{V}O_{2max}$, maximal oxygen uptake.
Data are presented as M ± SD.

$\dot{V}O_{2max}$ in equation 1 were lower than the minimum possible difference established, upper and lower limits of agreement in all 6-prediction equations were elevated.

Determining prediction equations for human body functions is a challenging task. These equations are based on a linear mathematical model; however, physiological human functions do not always display linear behavior. Moreover, since $\dot{V}O_{2max}$ is obtained after body systems reach extreme exercise conditions, rest parameters (anthropometric and lung function) may not be able to predict the response of body systems during exercise.

In contrast to other research,[5-7,22-24] the present study aimed to assess not only the relationship between estimated and measured $\dot{V}O_{2max}$ but also the agreement between them. Results found here confirm that a good relationship between estimated and measured values does not always mean good agreement. Indeed, the results of the present study demonstrate that estimated and measured values have a good relationship, but poor agreement.

In 1976, Wehr and Johnson[22] were the first to use a prediction equation to estimate $\dot{V}O_{2max}$ in 15 patients with respiratory disease, 6 with COPD, and 9 with restrictive diseases. The authors applied theoretical models of respiratory physiology and variables assessed at rest and during workload on a treadmill or cycle ergometer for 3.5 and 5 minutes, respectively, to obtain the prediction equation. Only 4 of the 6 COPD patients completed the study. Consequently, the results of this study cannot be compared with those obtained by these authors. In another study, Dillard et al[23] determined the prediction equation, using lung function at rest and maximal mouth inspiratory. These authors studied 20 male patients with COPD and the equation was based on D_LCO, maximal mouth respiratory pressure, and FEV_1. Good multivariate regression was

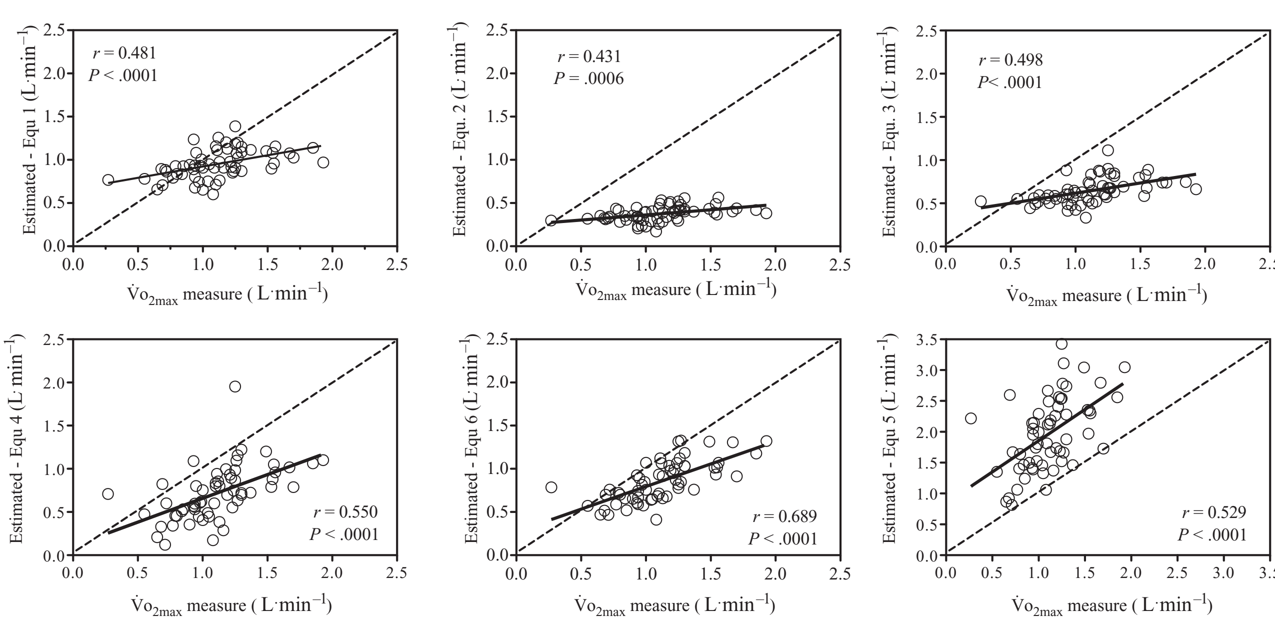

Figure 2. Correlation between direct maximal oxygen uptake ($\dot{V}O_{2max}$) measured and equations 1 to 6.

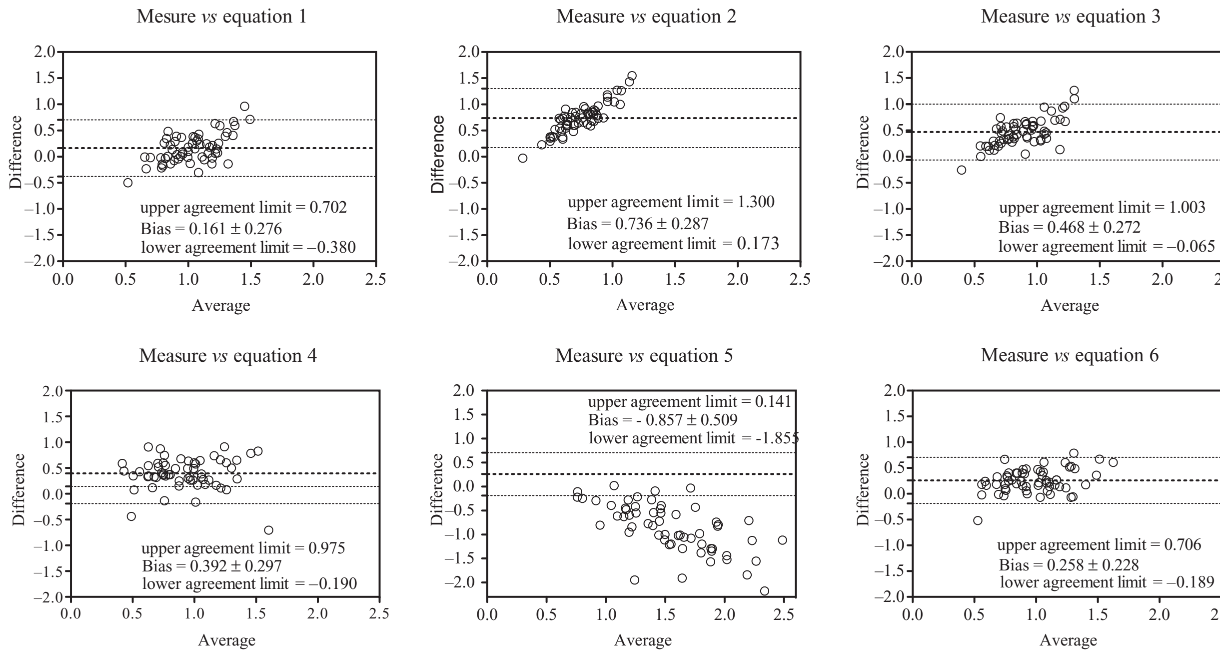

Figure 3. Bland-Altman between direct maximal oxygen uptake ($\dot{V}O_{2max}$) measured and equations 1 to 6. Agreement analyses between estimated $\dot{V}O_{2max}$ and direct $\dot{V}O_{2max}$ obtained in all 6 equations studied. Bias is the average of the differences ± SD between the 2 assay methods; upper and lower limits of agreement are mean bias ± 1.96 times its SD.

recorded between $\dot{V}O_{2max}$ and variables inserted into the model (R^2 = 0.911), but the study was restricted to establishing the prediction equation and no further analysis was carried out. LoRusso et al[24] analyzed the prediction equation in 146 COPD patients. Individuals were divided into mild (n = 64), moderate (n = 62), and severe groups (n = 20). The authors developed a multilinear regression model, testing lung function at rest for each group of patients. Six prediction equations based on each group classification demonstrated moderated to elevated correlation between maximal voluntary ventilation (r = 0.69-0.89) and $FEV_{1.}$ (r = 0.65-0.87). Nevertheless, selecting only a few variables to predict $\dot{V}O_{2max}$ is not appropriate. Maximal oxygen uptake results from a complex interaction involving cells as well as the cardiac and respiratory systems. Several factors can influence $\dot{V}O_{2max}$ results such as oxygen availability and blood oxygen-carrying capacity, which depend on available hemoglobin and cardiac function. Thus, the results of this study can be partially considered for analysis.

Cahalin et al[5] established the relationship between personal and anthropometric characteristics, pulmonary function tests at rest, and the 6MWT with $\dot{V}O_{2max}$ in 2 groups of male and female COPD patients. In the first group of 30 subjects (15 COPD), the authors performed multivariate analysis, while in the second group of 30 patients (19 COPD), a validation study was conducted. The 6MWT was the best single predictor of $\dot{V}O_{2max}$ and these authors proposed 4 equations, all of which included distance walked in the 6MWT. They found that the 6MWT predicted $\dot{V}O_{2max}$ with r = 0.73 and 0.67 for the first and second groups, respectively. Cross-validation of the prediction equation obtained from the first group and applied in the second group showed a coefficient of determination of 0.45, standard error of the estimate of 2.78 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$, and correlation coefficient of 0.67. The study obtained interesting results, including a new variable for the regression model (6MWT), and presented new hypotheses regarding predicted $\dot{V}O_{2max}$ in COPD. However, the prediction equation developed by these authors analyzed COPD patients without distinction between males and females. In another study, Carter et al[6] developed the prediction equation to estimate $\dot{V}O_{2max}$ in 90 male and 34 female COPD patients. They used variables from pulmonary function tests and distance walked in the 6MWT and introduced a new variable, 6MW distance versus body weight ($6M_{work}$) for multiple linear regression. This variable was published as a new method for describing bioenergetic movements.[17] The results showed a lower SEE (155.31) and good R^2 (0.7930); however, [AQ3] agreement analysis was not performed. Finally, Chuang et al[7] sought to validate their equation, which introduced the $6M_{work}$, in addition to testing all the equations presented by Cahalin et al[5] in 28 male COPD patients. Their predicted equation demonstrated that half of the patients showed differences between measured and estimated $\dot{V}O_{2max}$ greater than

0.150 L/min. Simple analysis of the differences between measured and estimated $\dot{V}O_{2max}$ using the equation predicted by these authors showed no significant difference (48 ± 217 mL·min^{-1}, $P = .25$). The authors also confirm, in contrast to findings obtained by Cahalin et al,[5] that introducing new variables such as FVC, FEV_1, and D_LCO does not improve the results of the prediction equation. Corroborating Cahalin et al[5] and Carter et al,[6] the study conducted by Chuang et al[7] did not analyze agreement between measured $\dot{V}O_{2max}$ and that estimated by the prediction equation. A potential limitation of this study is that only male patients with COPD were analyzed. However, considering that exercise response is similar between genders, this limitation could be minimal. Results confirm that estimated $\dot{V}O_{2max}$ is inaccurate for COPD patients.

The findings of this study have important clinical implications. Despite high costs and the need for specialized personnel to conduct CPET, physiological responses to exercise are so complex that it is impossible to accurately determine $\dot{V}O_{2max}$ using multiple regression formulas. The results obtained from CPET, specifically $\dot{V}O_{2max}$ associated to other variables, are normally used to make decisions regarding the implementation of physical exercise and rehabilitation programs. However, prescribing and assessing response to exercise cannot be based on discrepant values if $\dot{V}O_{2max}$, is measured.

The use of lung function at rest and submaximal exercise testing does not accurately determine $\dot{V}O_{2max}$. We, therefore, conclude that $\dot{V}O_{2max}$ cannot be estimated by prediction equations in male COPD patients and that CPET is absolutely necessary to know and use $\dot{V}O_{2max}$ in these patients.

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References

1. Holway ET, Basset DR, Welch HG. Criteria of maximal oxygen uptake: review and commentary. *Med Sci Sports Exerc.* 1995; 27:1292-1301.
2. Roca J, Whipp BJ, Agustí AGN, et al. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies ERS Task Force on Standardization of Clinical Exercise Testing. *Eur Respir J.* 1997;10:2662-2689.
3. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2003;167:211-277.
4. Gosselink R, Troosters T, Decramer M. Exercise testing: why, which and how to interpret. *Breathe.* 2004;1:121-129.
5. Cahalin L, Pappagianopoulos P, Prevost S, Wain J, Ginns L. The relationship of the 6-Min Walk Test to maximal oxygen consumption in transplant candidates with end-stage lung disease. *Chest.* 1995;108:452-459.
6. Carter R, Holiday DB, Stocks J, Grothues C, Tiep B. Predicting oxygen uptake for men and women with moderate to severe chronic obstructive pulmonary disease. *Arch Phys Med Rehabil.* 2003;84:1158-1164.
7. Chuang ML, Lin FI, Vintch JRE. Comparison of estimated and measured maximal oxygen uptake during exercise testing in patients with chronic obstructive pulmonary disease. *Int Med J.* 2004;34:469-474.
8. Sanchis J, Casan P, Castillo J, Gonzalez N, Palenciano L, Roca J. Normativa para la práctica de la espirometría forzada. *Arch Bronconeumol.* 1989;25:132-142.
9. Roca J, Sanchis J, Agustí-Vidal A, Rodríguez-Roisin R. Spirometric reference values for a Mediterranean population. *Bull Eur Physiopathol Respir.* 1986;22:217-224.
10. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis.* 1969;99:696-702.
11. Casan P, Mayos M, Gáldiz J, et al. Determinación de las presiones respiratorias estáticas máximas. Propuesta de procedimiento. *Arch Bronconeumol.* 1990;26:223-228.
12. Morales P, Sanchis J, Cordero PJ, Díez JL. Presiones respiratorias estáticas máximas en adultos. Valores de referencia en una población caucasiana mediterránea. *Arch Bronconeumol.* 1997;33:213-219.
13. Normativa sobre gasometría arterial. Recomendaciones SEPAR, n° 6. *Barcelona*: *Doyma*; 1987. [AQ4]
14. Brooks D, Solway S, Gibbons WJ. ATS statement on Six-Minute Walk Test. *Am J Respir Crit Care Med.* 2003;167:1287-1287.
15. Buthland RJA, Pang J, Gross ER, et al. Two-, six- and 12-min walking tests in respiratory disease. *BMJ.* 1982;284:1607-1608.
16. Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehab Med.* 1970;2:92-98.
17. Jones NL. *Clinical Exercise Testing.* 4rd ed. Philadelphia, PA: WB Saunders; 1997.
18. Chuang ML, Lin IF, Wasserman K. The body weight-walking distance product as related to lung function, anaerobic threshold and peak $\dot{V}O_2$ in COPD patients. *Respir Med.* 2001;95:618-626.
19. Garcia-Aymerich J, Serra I, Gómez FP, et al. Phenotype and course of COPD Study Group. Physical activity and clinical and functional status in COPD. *Chest.* 2009;136:62-70.
20. Bland JM, Altman DG. Statistical methods for assessing between two methods of clinical measurement. *Lancet.* 1986;1:307-310.
21. Pauwels RA, Buist AS, Calverley PMA, et al; on behalf of the GOLD Scientific Committee. GOLD: Global Initiative for Chronic Obstructive Lung Disease. National Institutes of Health, National Heart, Lung, and Blood Institute. *Am J Respir Crit Care Med.* 2001;163:1256-1276.
22. Wehr KL, Johnson RL Jr. Maximal oxygen consumption in patients with lung disease. *J Clin Invest.* 1976;58:880-890.
23. Dillard TA, Piantadosi S, Rajagopal KR. Determinants of maximum exercise capacity in patients with chronic airflow obstruction. *Chest.* 1989;96:267-271.
24. LoRusso TJ, Belman MJ, Elashoff JD, Koerner SK. Prediction of maximal exercise capacity in obstructive and restrictive pulmonary disease. *Chest.* 1993;104:1748-1754.

AUTHOR QUERIES

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AUTHROS: Guilherme Fregonezi, Vanessa Resqueti; Laura Vigil, Nuria Calaf, Pere Casan

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