Exercise tolerance in chronic obstructive pulmonary disease: importance of active and passive components of the ventilatory system

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Exercise tolerance in chronic obstructive pulmonary disease: importance of active and passive components of the ventilatory system. A. Loiseau, C. Dubreuil, P. Loiseau, J.C. Pujet, R. Georges, G. Saumon.
ABSTRACT: We investigated which components of ventilatory function are related to exercise tolerance in chronic obstructive pulmonary disease (COPD) patients. Physical characteristics, usual lung function, timing and neuromuscular components of ventilation were measured in 113 out-patients in whom FEV_1/VC was less than 75% of the predicted value and exercise was limited by breathlessness. These variables were used to predict the maximum work load during progressive bicycle exercise. The prediction was obtained using a stepwise procedure in men and women separately. Among the variables selected, age, body weight, FEV_1/VC, PI_{max}, and $P_{0.1}/VT/TI$ accounted for 79% of the variability in maximum performance in men. The predictive model was statistically verified and was stable. The mean prediction error was 12 Watts. Among these variables, $P_{0.1}/VT/TI$, PI_{max}, and FEV_1/VC were the main determinants of maximum work load (MWL). These results show that exercise limitation in COPD is related to impairment of both the active (inspiratory muscles) and passive (respiratory impedance) components of the ventilatory system. The same conclusions concerning passive components are proposed for women, despite a smaller population which prevented verification of the prediction.
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Maximal exercise performance has proved useful for assessment of respiratory impairment in patients with chronic obstructive pulmonary disease (COPD) [1]. Exercise hyperpnoea is the consequence of the interaction of chemical, neural, muscular, haemodynamic, and mechanical processes [2]. Exercise tolerance in COPD patients is only explained in part by usual assessment of ventilatory limitation (FEV_1/VC), static lung volumes, or $TLCO$ [1, 3–6]. Pulmonary haemodynamics do not appear important in limiting exercise in COPD patients [7, 8]. Other factors must therefore interfere. We hypothesize that neuromuscular drive and respiratory efficiency might be among these factors. For instance, maximum exercise may depend on the ability of inspiratory muscles to sustain the required ventilation. The importance of respiratory muscle fatigue as a component of exercise limitation has been demonstrated [9]. Recent studies have documented central neural failure during high ventilation and have acknowledged its role in ventilatory failure [10–12]. Based on this assumption one could expect that the maximum exercise performance could be more precisely predicted by taking into consideration additional factors such as occlusion pressure ($P_{0.1}$), respiratory timing (TI/T_{TOT}), inspiratory flow rate (VT/TI) [13], maximum inspiratory pressure (PI_{max}) [14], and respiratory impedance ($P_{0.1}/VT/TI$) [15, 16].

We investigated which components of ventilatory function are related to exercise tolerance in COPD patients. We selected a set of predicting variables measured at rest that might determine exercise performance, including physical characteristics, lung volumes, FEV_1, and estimates of respiratory drive. The respective importance of these factors in predicting exercise limitation in COPD patients was assessed using stepwise and ridge regressions. We found that respiratory muscle strength and respiratory impedance are important determinants of exercise tolerance in these patients.

Methods

Patients population

We selected 113 COPD out-patients (93 men, 20 women) with clinical and physiological evidence of chronic airflow limitation according to the criteria of the American Thoracic Society [17]. Twenty two also presented emphysema and 11 post-tuberculosis fibrotic lesions. Patients with acute bronchial infection, cardiovascular disease or history of asthma were excluded. None of these patients had received any drug during the two weeks prior to the study. In all patients, FEV_1/VC was

less than 75% of the predicted value and exercise was limited by breathlessness. 80% of patients presented objective evidence of exercise limitation of respiratory origin: maximal cardiac frequency during exercise was less than 80% of the predicted maximal value, maximal exercise ventilation was in keeping with FEV_1 [3]. Several factors might have influenced exercise limitation in others (such as cardiovascular factors, leg muscle fatigue, but also ventilatory limitation). Most of the subjects were smokers and 69% were still smoking an average of one pack of cigarettes per day. All patients were familiar with pulmonary function testing and gave informed consent for this study. The physical characteristics and lung function tests of the population are given in table 1. The predicted values for lung function tests are those of QUANJER *et al.* [18].

which provided a known torque against the electromagnetic brake.

Exercise protocol

Progressive exercise was performed at a cycling speed of about 50 rpm by 102 patients, after a 3 min rest. The work load was increased by 30 watt steps every 3 min until exhaustion. In 11 male patients, the work load was increased by 10 watt steps every minute until exhaustion and the exercise was performed in triplicate in the same week to determine intra-subject variability. Breathing patterns at rest, $P_{0.1}$ and PI_{max} were obtained during the resting period before exercising. They represented the mean of 6 to 10 non-consecutive breaths.

Table 1. – Physical and functional values in COPD patients

		Men (n=93)			Women (n=20)		
		mean	SEM	(range)	mean	SEM	(range)
Age	yrs	62	1.0	(22–77)	63	2.2	(49–80)
Height	cm	169	0.8	(151–184)	162	0.1	(154–170)
Weight	kg	67	1.2	(40–91)	56	2.6	(37–87)
VC	%pred*	62	2.6	(47–100)	74	5.8	(29–100)
FEV_1/VC	%	39	1.2	(20–71)	48	3.7	(19–83)
RV/TLC	%	54	0.9	(33–68)	56	1.7	(42–72)
Pao_2	kPa	9.2	0.16	(7.1–11.6)	9.6	0.21	(8.4–10.7)
$Paco_2$	kPa	5.3	0.07	(4.0–6.9)	5.2	0.12	(4.3–5.9)
Sao_2	%	93.5	0.4	(86–96)	94.5	0.4	(92–96)
PI_{max}	kPa	4.8	0.17	(2.0–8.3)	4.2	0.41	(2.2–9.0)
$P_{0.1}/VT/TI$	$kPa \cdot l^{-1} \cdot s$	0.41	0.017	(0.09–1.05)	0.54	0.068	(0.22–1.34)

*: percent of predicted value.

Methods

Static lung volumes were measured with a water-sealed spirometer (Spirotest 3, Jaeger, West Germany); residual volume was measured by helium dilution. Blood gases were determined from an arterialized ear lobe blood sample [19] at rest (IL213, Delhomme, Paris). An automatic apparatus was used to measure mouth occlusion pressure ($P_{0.1}$) [20]. Inspiratory resistance of the apparatus was $0.15 \ kPa \cdot l^{-1} \cdot s$ and the expiratory resistance $0.05 \ kPa \cdot l^{-1} \cdot s$. Maximal static inspiratory pressure (PI_{max}) was measured at FRC during total occlusion with a ±15 kPa pressure transducer (MP45, Validyne, Northridge, CA). Tidal volume (VT), inspiratory (TI) and expiratory (TE) times from the breath preceding occlusion were measured with a Fleish no. 3 pneumotachometer and a ±0.2 kPa pressure transducer (Validyne). Calibrations were made by the usual techniques: a static calibration for $P_{0.1}$ and PI_{max} transducers, and a dynamic calibration with a calibrated syringe for the pneumotachometer [21]. Exercise was performed using a cycle ergometer that dissipates the work of pedalling against an electromagnetic brake (Gauthier EPC 7701, Paris, France). It was calibrated by means of a standard weight attached to a pedal

Statistical analyses

Data are presented as mean±SEM unless indicated otherwise. The relation between variables was obtained by linear regression using a least square method. Stepwise multiple regression, and ridge procedure (22, 23, 24) were used to determine a predictive equation for maximum performance in men and women separately. Maximum performance was defined as the largest work load performed allowing longer exercise than half a step duration. The analyses were performed using STATGRAPHICS software (STSC, Rockville, Maryland, USA) on an IBM PC computer.

Stepwise regression consists of selecting those variables which provide the best information for the prediction using the partial correlation coefficients as a measure of the predictor importance of variables. The coefficient of determination (R^2) represents the overall fraction of variability for the predicted variable that is explained by the regression model. However, when many predictor variables are interdependent, the regression coefficients may not be stable from one population sample to another and cannot be used in a predictive mode. Thus, a further analysis was performed. Ridge regression [23]

was used to verify the stability of regression coefficients. The reliability of the predictive equation was tested using another sample of the patient population.

The relative importance of each of the components in the predictive equation was approximately determined from the standard partial regression coefficient values [24].

The 95% confidence interval (± 2 SD) for the predicted-observed MWL relationship was used as a criterion of the soundness of classification; the patients within the confidence interval were considered as correctly classified. The confidence interval was obtained from the mean of the intra-subject MWL standard deviation.

The COPD population was divided into 2 groups according to sex (group A: 20 women, group B: 93 men). Intra-subject variability of MWL was assessed in 11 subjects in group B (subgroup B3). The other subjects in group B (n=82) were randomly allocated to 2 sample groups of equal size and identical MWL distribution (subgroup B1 and B2). Group B1 (n=41) was used to establish the prediction and groups B2 and B3 (n=52) were used to verify the prediction model.

"Predictor" variable set

Age, height and body weight were chosen because we felt that these factors account for the variability in the subject's physical aptitude for exercise. VC (% predicted) and RV/TLC were selected because they are indexes of ventilatory capacity and thorax shape while FEV_1/VC reflects the resistive load of the ventilatory system during expiration. Pao_2, Sao_2 and $Paco_2$ were selected as indexes of hypoxaemia and capnia. Mean inspiratory flow (V_T/T_I) and the inspiratory duty cycle (T_I/T_{TOT}) were chosen as components of ventilation depending on neu-

ral events. The inspiratory effectiveness of muscle contraction was taken into account by means of PI_{max} and, passive inspiratory mechanical impedance of the ventilatory system by means of the effective inspiratory impedance ($P_{0.1}$/V_T/T_I). $P_{0.1}$ was chosen as an index of inspiratory neuromuscular drive.

Results

Physical characteristics and the results of lung function testing in COPD patients are given in table 1. Patients had decreased vital capacity ($64\pm2.4\%$ predicted value), airway obstruction (FEV_1/VC=$41\pm1.2\%$) and increased RV/TLC ratio ($54\pm1.0\%$). Analyses of blood gases revealed hypoxaemia (Pao_2=9.3 ± 0.14 kpa), decreased haemoglobin saturation (Sao_2=$93.7\pm0.34\%$) and normocapnia ($Paco_2$=5.3 ± 0.05 kpa). The MWL according to our definition ranged from 0 to 120 Watts. Only 2 men and 2 women were unable to perform on the lowest work load for less than 1 min 30 (0 Watt). The results of lung function were not significantly different between the B1 and B2 groups. Significant correlations were observed between MWL and age, FEV_1/VC, RV/TLC, $P_{0.1}$/V_T/T_I, and PI_{max} (p<.001).

Stepwise procedure

The stepwise multiple regression selected age, FEV_1/VC, weight, PI_{max} and $P_{0.1}$/V_T/T_I from the "predictor" variable set for men. Values and levels of significance of the regression coefficients are given in table 2. 79% of the variability in performance was explained by this model, however, this figure might be due in part to some interdependence between the predictor variables.

Table 2. – Stepwise regression

a) In men: group B1 (n=41)

Y-intercept=14W	(Multiple) R^2=0.786				
			Variable		
	PI_{max} kPa	Age yrs	$P_{0.1}$/V_T/T_I kPa·l^{-1}·s	FEV_1/VC %	Weight kg
Regression coefficient	5.81	-0.60	-83.7	1.39	0.763
SD	1.56	0.295	13.67	0.232	0.244
	p<0.001	p<0.05	p<0.001	p<0.001	p<0.004

b) In women: group A (n=20)

Y-intercept=172W	R^2=0.798		
		Variable	
	Age yrs	$P_{0.1}$/V_T/T_I kPa·l^{-1}·s	FEV_1/VC %
Regression coefficient	-1.60	-75.56	0.525
SD	0.341	10.95	0.20
	p<0.001	p<0.001	p<0.02

Predicted variable: maximal work load (Watt); "Predictor" variable set: age, height, weight, VC% pred, FEV_1/VC, RV/TLC, V_T/T_I, T_I/T_{TOT}, Pao_2, $Paco_2$, Sao_2, $P_{0.1}$, PI_{max}, $P_{0.1}$/V_T/T_I

Correlation analysis showed significant interdependence between FEV_1/VC and age only ($p<0.05$) and a borderline interdependence between PI_{max} and $P_{0.1}/VT/TI$ ($p<0.06$). The ridge trace did not reveal instability in the coefficients. $P_{0.1}/VT/TI$, FEV_1/VC and PI_{max} were the most important factors in the prediction equation.

In women, the same amount of MWL variability was explained by age, FEV_1/VC and $P_{0.1}/VT/TI$ (80%). Values and levels of significance for the regression coefficients are given in table 2. However, the small size of the population sample for women prevented in depth analysis.

The intra-subject variability (SD) of MWL was independent of the MWL level. The mean of the intra-subject standard deviations was equal to 6 Watts. As it was far smaller than the work load corresponding to a single step, we refrained from testing the reproducibility of the 30 W/3 min protocol.
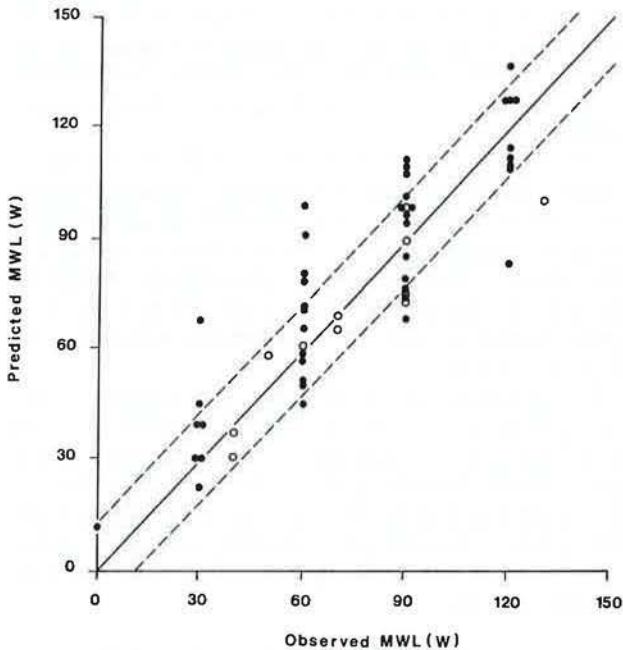

Fig. 1. – Plot of maximum work load (MWL) observed during progressive exercise in COPD patients *vs* MWL predicted according to the multiple linear regression equation. Closed circles correspond to the 30 W/3 min and open circles to the 10 W/1 min progressive protocols for groups B2 and B3 (52 patients). This population sample was used to verify the prediction equation established with the sample group B1 (41 patients) with similar MWL distribution.

Validity of the model

The prediction equation was verified using the samples B2 (n=41) and B3 (n=11) (figure 1). Prediction error ranged from -38 W to +37 W (mean value=12 W). There was no major difference in the prediction error when the results of the two exercise protocols were compared (10 W or 30 W step load). There was also no significant difference in the prediction when comparisons were made using the predictive equation from the stepwise regres-

sion or the ridge coefficients. The percentage of patients who were correctly classified was 66% in sample B2 (figure 1; closed circles). The maximum work load was underestimated for less than a step (23 W) in 4 patients, and overestimated in 10 patients. Nevertheless, it should be emphasized that in 8 out of 10 of the latter, the predicted value could be accurate, since the predicted maximum work load was less than the value for the next step in the protocol. For example, a subject with a predicted maximum workload of 115 W and with an observed performance of 90 W could actually be capable of performing 115 W. However, since the intermediate levels were not tested in these patients, the observed MWL may have been underestimated. Thus, the percentage of patients with good prediction lies between 66 and 85% (mean 75%). The reliability of the prediction equation was similar for the subjects in sample B3 (8 out of 11 correct predictions).

Discussion

The relationship between maximum exercise and pulmonary function measurements in COPD patients at rest was always found to be weak [1, 3–5]. The best prediction for MWL was obtained using the following relationship [1]: MWL ($kgm \cdot min^{-1}$)=563-5.4 Age+142 FEV_1+7.5 $TLCO$; $R^2=0.54$). This model was not verified with another group of patients. The present study shows that the inclusion of respiratory muscle strength and impedance of the ventilatory system as additional factors improves MWL prediction ($R^2=0.79$).

Methodological considerations

Various prerequisites must be fulfilled to establish a valid predictive model: physiological significance of the retained variables as will be discussed, adequacy of the signs of the regression coefficients, accuracy of the prediction (R^2), absence of interdependence between the retained variables (assessed by the stability of the regression coefficients) and validation of the model using another sample of patients from the same population.

The algebraic sign (+ or -) of each multiple regression coefficient was found to be as expected according to the physiological effect of the variable on MWL (inverse or positive relation): it corresponds to a positive effect on MWL for PI_{max}, FEV_1/VC and weight, and to a negative effect for age and $P_{0.1}/VT/TI$. Despite the interdependence of FEV_1/VC and age, the stability of the regression coefficients was correct as assessed by the ridge trace. Verification of the MWL prediction in samples B2 and B3 confirmed the stability of the model since the MWL of about 75% of patients were correctly predicted. The accuracy of the prediction (12 watts) is acceptable since variability is expected to be large in COPD patients weakened and stressed by their disease.

Physiological considerations

The components of the MWL prediction equation are more or less directly related to three main determinants

of exercise aptitude that is, the physical ability to perform exercise and particularly muscle mass, the passive respiratory system, the active respiratory system.

a. Physical ability is accounted for in the prediction equation by age and body weight which are regularly found to be predictors of $\dot{V}o_2$max, which in turn, is directly related to muscular ability in healthy non obese subjects [25]. The observation that age affects MWL in normal subjects, was also observed in this series of COPD patients (despite large variations in disease progression). Age probably reflected leg muscular weakness and articular stiffness in these sedentary patients. Body weight, in non obese COPD subjects, is indicative of muscle mass [25], an important factor in exercise capacity. These patients, and particularly those with emphysema, often have muscle atrophy because of nutritional depletion [26].

b. Airway obstruction is accounted for in the regression by FEV_1/VC which indirectly quantifies the increase in expiratory impedance. In COPD patients, maximum exercise ventilation usually approaches, or may even exceed, maximal voluntary ventilation [3, 27] and is limited by the maximal expiratory flow rate [28]. During incremental exercise testing, the need for increased airflow soon forces the subject to reach the maximum value obtained during a forced volitional effort for a given lung volume [29, 30]. This mechanical limitation of maximum exercise ventilation in COPD patients is the consequence of both airway obstruction and of hyperinflation.

c. The efficiency of the active respiratory system depends on both the inspiratory neuromuscular drive and the impedance which opposes inspiration. $P_{0.1}/V_T/T_I$ may be considered to be an index of the effective inspiratory impedance [15, 16] and PI_{max} as a measure of inspiratory muscle strength [14]. Both parameters are related to the efficiency of the active ventilatory system and also thorax shape. PI_{max} appears to be a valuable parameter to quantifying loss of respiratory muscle efficiency as a consequence of hyperinflation. During hyperinflation, the inspiratory muscles are in a less efficient force-length relationship due to a shorter operating length. As the diaphragm flattens, greater activity of the inspiratory intercostal-accessory muscles is required to provide an increase in ventilation [31].

The factors retained in the prediction of MWL are therefore directly or indirectly related to systemic or respiratory muscles and to the impedance of the ventilatory system. These findings are consistent with those of KILLIAN and coworkers [32, 33] who demonstrated that these same factors are involved in the development of exercise dyspnoea. In conclusion, these factors therefore appear to be of importance in determining maximum performance and should be taken into consideration when searching for therapies (nutrition, muscle contractility, dyspnoea sensation...) aiming at increasing exercise tolerance in COPD patients.

Other factors to be considered

Our prediction of MWL is still imperfect. It indicates that other factors need to be considered. The stress resulting from a relatively strenuous exercise and leg weakness may play a role in interrupting exercise. These factors are not easy to quantify due to the absence of corresponding indexes at rest. Dyspnoea tolerance might also be a factor to take into consideration because it would account for the subjective components of effort tolerance. The model would perhaps be improved by the addition of TLCO. TLCO reflects the effectiveness of gas exchange and thus might be a valuable predictor of how the respiratory system allows the patient to sustain effort. It has been found to be correlated with exercise tolerance [1, 5] and is probably one of the factors that could improve the prediction from measurements performed at rest. Although cardiovascular factors do not seem to affect maximum exercise to a large extent in COPD patients [7, 8], they might provide additional information explaining exercise limitation.

Arterial blood gases were not retained in stepwise regression for evaluation. This confirms the previous observations that blood gases are not closely related to exercise performance [34]. Metabolic acidosis does not usually occur during maximum exercise in COPD. The maximum blood lactate concentration remains in the normal resting range [35, 36]. Despite hypoxaemia, oxygen delivery to exercising muscle is usually maintained [1].

The multiple linear regression model is limited to additive effects of predictor variables, whereas interactive effects are perhaps more plausible on physiological grounds. Integration of interactive effects in an explicative model would therefore be advantageous. However, this implies that all possible relations between the variables studied are known. This problem however is far from being solved.

In conclusion, this study shows that maximum exercise performance in COPD patients is related to both active and passive components of the ventilatory system and probably depends on them. The clinical relevance of this finding is that therapies aiming at increasing respiratory muscle strength and decreasing respiratory impedance might be useful for submaximal exercise tolerance in these patients.

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RÉSUMÉ: Chez 113 malades ambulatoires souffrant de BPCO, nous avons recherché les composantes de la fonction ventilatoire qui influencent la performance maximale à l'effort (MWL) durant un exercice progressif. Des paramètres d'aptitude physique et de fonction pulmonaire ainsi que les composants actifs et passifs de la ventilation ont été sélectionnés comme prédicteurs possibles de MWL. Chez tous ces patients, le VEMS/CV était inférieur à 75% de sa valeur théorique et l'exercice était limité par une dyspnée d'effort. La prédiction de MWL a été effectuée séparément chez les hommes et les femmes, en utilisant une régression multiple pas à pas. La variabilité de la MWL est expliquée pour 79% par l'âge, le poids, le VEMS/CV, la Pr_{max} et $P_{0.1}/VT/TI$ chez les hommes. La vérification statistique du modèle a montré que la prédiction de MWL était stable avec une erreur de prédiction de 12 Watts. $P_{0.1}/VT/TI$, la Pr_{max} et le VEMS/CV étaient les déterminants majeurs de la MWL. Ces résultats montrent que la limitation ventilatoire à l'exercice chez les BPCO est en partie déterminée par les composants actifs (force musculaire inspiratoire) et passifs (impédance) du système ventilatoire. La même conclusion a été obtenue pour les femmes en ce qui concerne les composants passifs.

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