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Prediction of Maximum Exercise Tolerance in Patients with COPD*

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Exercise tolerance in patients with COPD is difficult to predict from measurements of lung function. We examined multiple physiologic and psychosocial variables in an attempt to predict exercise performance in a group of patients with COPD enrolled in a clinical trial of pulmonary rehabilitation. A total of 119 patients ($FEV_1 = 1.41 \pm 0.64$ L) were divided randomly into either a study group (group A, n=58) or validation group (group B, n=61). Stepwise multiple regression in group A revealed that peak oxygen uptake (peak $\dot{V}O_2$) was predicted best by the following equation: Peak $\dot{V}O_2$ (L/min) = (0.0327 × DCO) + (0.0040 × MVV) − (0.0156 × peak-exercise VD/VT) + (0.0259 × resting $\dot{V}E$) + 0.848; r = 0.90; SE = 0.233 L/min. This equation was then cross-validated in group B. It demonstrated excellent validity: measured peak $\dot{V}O_2$ (L/min) = (1.13 × predicted peak $\dot{V}O_2$) − 0.0891; r = 0.90; SE = 0.239 L/min. We conclude that exercise tolerance was predicted reasonably well from measurements of lung function and gas exchange in this group of patients with COPD. However, the variability of the prediction would limit its usefulness in individual patients. *(Chest 1991; 100:307-11)*

BDI = Beck depression inventory; CES-D = Center for Epidemiologic Studies Depression Scale; DCO = diffusing capacity of carbon monoxide; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure (used synonymously with PIP); MVV = maximal voluntary ventilation; PEFR = maximal expiratory flow; PIFR = maximal inspiratory flow; QWB = quality of well-being; RV = residual volume; RV/TLC = ratio of residual volume to total lung capacity; SaO_2 = oxygen saturation of arterial blood

Maximum exercise tolerance in patients with COPD has multiple determinants and is difficult to predict from measurements of resting lung function. Measurements of maximum exercise tolerance have been reported to be useful in preoperative evaluations,[1] disability evaluations,[2] establishing exercise training regimens,[3] and determining the cause of exertional symptoms.[4,5] In addition, understanding the factors which predict exercise capacity may provide clues to a better understanding of physical activity limitations in patients with COPD.

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Previous studies in patients with COPD have indicated that ventilatory limitation is a primary determinant of exercise tolerance.[5] However, individual pulmonary function parameters (*eg*, FEV_1) explain only about half of the variance in measured exercise tolerance.[6,7] Several published studies[6-13] have used multiple regression techniques to examine how well different combinations of physiologic variables can predict maximum oxygen consumption (peak $\dot{V}O_2$) or maximum workload. These studies, with differences in patient selection and predictor variables, have been able to explain between 53 and 92 percent of the variance in measured exercise tolerance.

For many patients with COPD, psychosocial characteristics may interact with physiologic abnormalities to limit physical work capacity. To date, published studies have not closely examined the role of psychosocial variables in the prediction of peak $\dot{V}O_2$ in patients with COPD.

This study uses data from a clinical trial of rehabilitation in COPD. The purposes of the analysis were the following: to examine how well exercise tolerance, specifically peak oxygen uptake (peak $\dot{V}O_2$), can be predicted from a combination of physiologic and psychosocial measurements, and to provide insight into factors determining and limiting exercise tolerance in these patients.

Methods

Patient Population

One hundred nineteen patients with COPD served as subjects. These patients were studied on entry to a clinical trial evaluating pulmonary rehabilitation. All patients met the following criteria: (1) clinical diagnosis of COPD confirmed by history, physical examination, abnormal spirometry, and chest roentgenogram; (2) no other significant lung disease; (3) clinically stable on an acceptable medical regimen; and (4) no unstable cardiac disease or other medical problem which would limit participation in the rehabilitation program. All patients gave informed consent as approved by the UCSD Human Subjects Committee.

Measurements

Prior to beginning the clinical trial, all patients underwent baseline assessment with extensive physiologic and psychosocial tests.

Pulmonary Function: Each patient underwent pulmonary function testing including spirometry, lung volumes by body plethysmography, DCO, 12-s maximum voluntary ventilation, MIP at RV, MEP at

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TLC, PIFR, and PEFR. Spirometry and lung volumes were obtained before and 20 min after two inhalations of metaproterenol (postbronchodilator measurements were used in this analysis). Testing and quality-control procedures followed standard and recommended methods.[14] Normal values used in this study were those of Morris and co-workers[15] for spirometric data, and those of Bass and co-workers[16] for flow-volume parameters.

Exercise Tolerance and Gas Exchange: Each patient performed an incremental, symptom-limited exercise test to the maximal tolerable level on a treadmill. Treadmill walking was begun at 1.0 mph with no grade, increased by 0.5 mph increments to 3.0 mph, and then increased in percent-grade by either 2 or 4 percent increments up to 24 percent-grade. Prior to this test, a radial arterial catheter was inserted percutaneously for arterial blood sampling at rest and during exercise. Arterial oxygen saturation was monitored continuously by ear oximetry, and measurements were recorded simultaneously with each arterial blood sample. Electrocardiography was monitored prior to and during the exercise test, and blood pressure was taken manually at periodic intervals. Expired gases were monitored and analyzed by computer for calculation of $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$, and V_D/V_T (as calculated from measured $PaCO_2$ and P_ECO_2). At the end of the test, patients rated their symptoms of breathlessness and fatigue. Peak exercise was defined as the highest work level reached during the incremental exercise test. Patients were included in the analysis without respect to submaximal effort, cardiac rate limitation, or ventilatory limitation to exercise.

Psychosocial: The following psychosocial measurements were included in this analysis:

(1) Quality of Well Being Scale (QWB), a subcomponent of the General Health Policy Model developed by Bush and colleagues.[17] This measure provides an index value for health status on a scale ranging from 0 (for death) to 1.0 (for optimum health). The index has subscales for mobility, physical activity, social activity, and symptoms.

(2) Self-efficacy measures in which patients rate the strength of their expectation to perform various behaviors requiring physical and/or emotional stamina (*eg*, exertion, walking, climbing, pushing, stress, lifting, and anger).[18]

(3) Two depression scales: the Centers for Disease Control, Center for Epidemiologic Studies Depression Scale,[19] and the Beck Depression Inventory.[20]

(4) A shortness of breath questionnaire, in which patients rate their breathlessness on a scale of 0 to 4 for various physical activities.[21]

(5) Selected social parameters including alcohol use and social living status, obtained from a screening questionnaire.

Statistical Analysis

For analysis, the 119 patients were first divided randomly into either a study group (group A, n = 58) or validation group (group B, n = 61). Stepwise multiple regression[22] was performed on the 58 group A patients to determine the best predictors of peak $\dot{V}O_2$ from selected independent variables (see Table 1). The stepwise routine used a combination of forward selection based on zero-order relationships and backward elimination based on tolerance. Computations were made with the BMDP P2R program. Some measurements could not be obtained in 4 of these 58 patients because of inability to breath-hold for the DCO measurement (n = 3), or no expired gas analysis because of supplemental oxygen use (n = 1). This analysis identified four variables as the best combination of predictors of peak $\dot{V}O_2$ (DCO, MVV, peak-exercise V_D/V_T, and resting $\dot{V}_E$). The multiple regression was then performed on the 54 patients in whom we were able to obtain measurements of peak $\dot{V}O_2$ plus all four of these independent variables. This prediction equation from group A was then cross-validated in group B patients, comparing the peak $\dot{V}O_2$ predicted from the equation with the peak $\dot{V}O_2$ directly measured from expired gases.

Table 1—*Independent Variables and their Correlations with Peak $\dot{V}O_2$ in Group A (total n = 58)*

PULMONARY FUNCTION	r	n
FEV_1	0.70	58
FEV_1 (% predicted)	0.53	58
FVC	0.56	58
FVC (% predicted)	0.42	58
PIFR	0.31	56
PEFR	0.53	58
PEFR (% predicted)	0.46	58
VC	0.51	58
RV/TLC	−0.62	58
MIP	0.53	58
MEP	0.42	58
MVV	0.64	57
Exercise/Gas Exchange		
Resting		
$\dot{V}_E$	0.05	57
PaO_2	0.36	58
$PaCO_2$	−0.39	58
V_D/V_T	−0.49	57
% SaO_2	0.36	58
Peak exercise		
PaO_2	0.56	57
$PaCO_2$	−0.39	57
V_D/V_T	−0.73	57
DCO	0.82	55
GENERAL/PSYCHOSOCIAL		
Age	0.14	58
Height	0.24	58
Alcohol use	0.12	56
Living alone	−0.05	58
Quality of well-being	0.11	58
CES-D depression	0.15	58
BDI depression	−0.09	57
Self-efficacy for:		
Walking	0.47	58
Climbing	0.32	58
Pushing	0.23	58
Stress	−0.12	58
Anger	0.08	58
Lifting	0.40	58
Exertion	0.06	58
Perceived fatigue	0.29	57
Perceived dyspnea	0.10	57
Shortness of breath with:		
Walking	−0.28	57
Daily activities	−0.32	58
Limitation from dyspnea	−0.31	56
Fear of dyspnea	0.05	54

RESULTS

Selected pulmonary function and exercise test results are presented in Table 2 for both the study group (group A, n = 58) and validation group (group B, n = 61). There were no significant differences by Student's *t*-tests between the two groups for any of the variables examined.

The multiple regression analysis to predict peak $\dot{V}O_2$ from the 54 group A patients generated the following prediction equation:

Table 2—*Selected Results for Patients Randomly Assigned to the Study (A) and Validation (B) Groups**

Variable	*Group A* (n = 54-58)	*Group B* (n = 56-61)
Males/Females	40/18	47/14
Age, yr	62.0 ± 7.0	63.2 ± 7.4
FEV_1, L	1.44 ± 0.62	1.40 ± 0.67
FVC, L	3.14 ± 0.85	3.12 ± 0.90
RV/TLC, %	55.3 ± 11.1	55.9 ± 10.7
Dco, ml/min/mm Hg	14.8 ± 7.5	13.4 ± 6.7
MVV, L/min	48.8 ± 23.6	46.2 ± 24.8
Rest VD/VT, %	49.4 ± 8.4	47.2 ± 8.6
Exercise VD/VT, %	42.1 ± 12.3	42.3 ± 11.0
MIP, cm H_2O	88.4 ± 29.5	91.9 ± 27.8
Rest $\dot{V}_E$, L/min	15.0 ± 4.1	13.8 ± 3.0
Peak $\dot{V}O_2$, L/min	1.25 ± 0.50	1.23 ± 0.54

*Values are means ± SD. There were no significant differences by Student's *t*-testing between groups A and B for any of the variables.

Equation 1: (group A, n = 54)

$$\text{Peak } \dot{V}O_2 \text{ (L/min)} = (0.0327 \times D_{CO}) + (0.0040 \times MVV) - (0.0156 \times \text{peak-exercise } V_D/V_T) + (0.0259 \times \text{resting } \dot{V}_E) + 0.848.$$
$$(r = 0.90;\ S_E = 0.233 \text{ L/min}).$$

Results of the cross-validation of equation 1 in group B patients are presented in Figure 1, which compare peak $\dot{V}O_2$ predicted from equation 1 with that measured from expired gases. The regression equation describing this relationship was:

Equation 2:

$$\text{Measured peak } \dot{V}O_2 \text{ (L/min)} = (1.13 \times \text{predicted peak } \dot{V}O_2) - 0.089.$$
$$(r = 0.90;\ S_E = 0.239 \text{ L/min}).$$

Using only resting pulmonary function parameters as independent variables, the best regression equation to predict peak $\dot{V}O_2$ was:

Equation 3: (group A, n = 54)

$$\text{Peak } \dot{V}O_2 \text{ (L/min)} = (0.0441 \times D_{CO}) + (0.0067 \times MVV) + 0.282.$$
$$(r = 0.86;\ S_E = 0.266 \text{ L/min}).$$

Finally, we repeated the linear regression analysis in all subjects (groups A and B together) to generate a prediction equation for peak $\dot{V}O_2$ which would best estimate peak $\dot{V}O_2$ for the entire COPD patient sample. This prediction equation was minimally different from the equation generated from group A alone (equation 1):

Equation 4: (groups A and B, n = 110)

$$\text{Peak } \dot{V}O_2 \text{ (L/min)} = (0.0316 \times D_{CO}) + (0.0042 \times MVV) - (0.0152 \times \text{peak-exercise } V_D/V_T) + (0.0283 \times \text{resting } \dot{V}_E) + 0.818.$$
$$(r = 0.91;\ S_E = 0.225 \text{ L/min}).$$

Discussion

The results of this study demonstrate that peak $\dot{V}O_2$ can be predicted with excellent accuracy (r = 0.90; SE = 0.233 L/min) in a group of patients with COPD from the independent variables utilized in this analysis. In addition, the prediction equation obtained proved to have excellent validity when tested in a similar, but separate, group of patients.

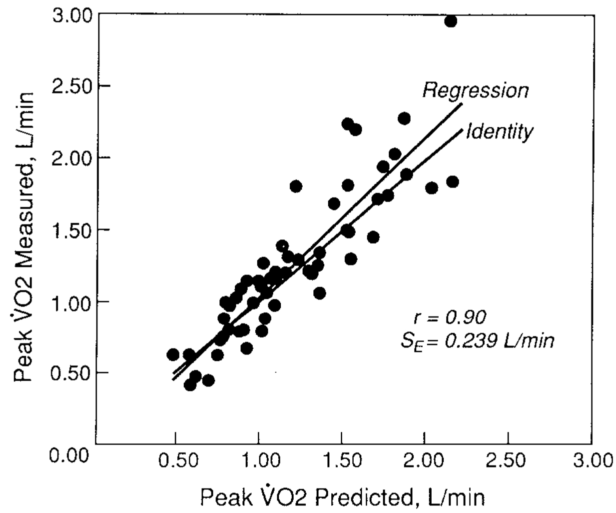

Figure 1. Group B validation. The measured peak $\dot{V}O_2$ is compared to the peak $\dot{V}O_2$ predicted from equation 1 in group B patients. The regression line (equation 2) and line of identity are noted. SE = standard error of the estimate.

The combination of independent variables found to be most predictive of peak $\dot{V}O_2$ were Dco, MVV, peak-exercise VD/VT, and resting $\dot{V}_E$. Equation 1 accounts for 81 percent of the variance in measured peak $\dot{V}O_2$, both in the group of patients from which it was derived (group A) and in the separate group of patients used for validation (group B). However, despite its overall accuracy, the variability of this prediction equation (SE = 0.239 L/min) may limit its usefulness in individual patients, as the 95 percent confidence interval of the prediction (1.96 × SE = ± 0.468 L/min) represents 38 percent of the average peak $\dot{V}O_2$ in these patients.

The reasons for trying to predict peak $\dot{V}O_2$ from measures of resting pulmonary function are multiple. Patients could possibly be saved time, expense, and invasive procedures if an accurate prediction of their maximum exercise tolerance could be made based upon resting pulmonary function parameters. Reasonably accurate prediction equations could also be used to determine if the measured peak $\dot{V}O_2$ is consistent with the patient's physiologic status. This might indicate a need for further evaluation of the patient with "unexplained" exercise limitation in an individual whose exercise tolerance is reduced out of proportion to that predicted from resting pulmonary function. This might be especially helpful in the area of disability evaluation.

It should be noted that nine patients of the original 119 were omitted from the analysis due to severe hypoxemia requiring supplemental oxygen with exercise. In spite of this, some parameters of gas transfer and gas exchange (DCO and VD/VT) remained important predictors of exercise tolerance, suggesting that gas exchange is important in determining exercise limitation in these patients with COPD.

None of the psychosocial variables measured in this study were found to be significant predictors of peak $\dot{V}O_2$ once variance associated with physiologic variables was removed. Using multiple regression analysis, Mahler and Harver[6] found that the baseline dyspnea index was an important predictor of peak $\dot{V}O_2$ in a group of patients with COPD. In the present study, neither the measures of perceived breathlessness or fatigue during exercise nor the reported shortness of breath with physical activities added significantly to the overall prediction equation. The correlations between individual predictor variables and peak $\dot{V}O_2$ were only slightly lower in the present study than those reported in the study of Mahler and Harver,[6] although the present study used additional independent variables (*eg*, VD/VT) which turned out to be more important in the multiple regression equation.

Most similar published studies have examined only patients with COPD.[6,9,10-12] Two studies[8,13] examined patients with mixed respiratory diseases with ventilatory limitation to exercise, and one study[7] examined both patients with COPD and healthy subjects. In general, the methodology used in these other studies was similar to that used in the present one, namely retrospective multiple regression analysis of different parameters of resting and exercise pulmonary function to generate one or more prediction equations of either peak $\dot{V}O_2$ or maximum work load. Differences in results could be related to differences in patients (*eg*, disease severity) and to the specific variables examined. For instance, the degree of expiratory obstruction is variable in these other studies, with the mean FEV_1 between 1.22 L and 1.85 L. Mean peak $\dot{V}O_2$ of the different patient groups varied from 0.97 L/min to 1.80 L/min. The prediction equations generated, however, were more similar than different, with most containing a measure of expiratory flow and a measure of either gas transfer or gas exchange. The prediction equations explained between 79 and 91 percent of the variance in measured peak $\dot{V}O_2$ in different patient populations, although one study of patients with more severe expiratory obstruction could explain only 53 percent of the variance in measured peak $\dot{V}O_2$.[10]

Dillard and co-workers[9] demonstrated a strong correlation between peak $\dot{V}O_2$ and MIP (referred to as PIP), as well as power output, $\dot{V}E$ max, DCO, and FEV_1. The high correlation ($r=0.82$) between MIP and peak $\dot{V}O_2$ led the authors to conclude that inspiratory strength may be an important determinant of exercise capacity in patients with COPD. Our study found that, although MIP was significantly correlated with peak $\dot{V}O_2$ ($r=0.47$), it was not one of its most significant determinants. In our prediction equation, MVV may well explain the variance in peak $\dot{V}O_2$ accounted for by MIP and FEV_1, as MVV depends upon both inspiration and expiration. However, the patients in the Dillard study had less severe disease (mean $FEV_1 = 1.72$ L) than the patients in our study (mean $FEV_1 = 1.45$ L).

When only resting pulmonary function parameters were used in our analysis, the multiple regression equation accounted for 74 percent of the variance in the predicted peak $\dot{V}O_2$. In our patient population with moderately severe expiratory obstruction and higher VD/VT measurements, resting VD/VT was not as important as peak-exercise VD/VT in predicting differences in exercise capacity. This may be because there is less variability in resting VD/VT measurements for patients with more severe expiratory obstruction and higher resting VD/VT measurements. For our patients, the variability in the VD/VT measurement increased with exercise. Therefore, in patients with more severe COPD, resting VD/VT may be less discriminating in predicting differences in peak $\dot{V}O_2$; examining VD/VT at peak exertion may be more important in the prediction of peak $\dot{V}O_2$. On the other hand, resting VD/VT may be more helpful in predicting the peak $\dot{V}O_2$ in a more heterogeneous population (*ie*, one including normal subjects or patients with pulmonary diseases other than COPD).

In summary, maximum exercise tolerance is predicted reasonably well from measurements of lung function and gas exchange in this group of patients with moderate to severe COPD. The variability of this prediction, however, would limit its usefulness in individual patients. The most consistent predictors of peak $\dot{V}O_2$ were measurements of expiratory flow and gas exchange; none of the psychosocial variables added significantly to the accuracy of the prediction of peak $\dot{V}O_2$.

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