Multivariable Assessment of the 6-min Walking Test in Patients with Chronic Obstructive Pulmonary Disease

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Functional exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) is often assessed by the 6-min walking test (6MWT). To assess if the use of multiple factors adds to walking distance in describing performance in the 6MWT, an exploratory factor analysis was performed on physiological measurements and dyspnea ratings recorded during testing. Eighty-three patients with mild to severe COPD performed repeated 6MWTs before inpatient pulmonary rehabilitation. Factor analysis on 15 variables yielded a stable four-factor structure explaining 78.4% of the total variance. Recorded heart rate variables contributed to factor 1 (heart rate pattern), walking distance, heart rate increase, and decrease contributed to factor 2 (endurance capacity), oxygen desaturation variables contributed to factor 3 (impairment of oxygen transport), and dyspnea and effort variables contributed to factor 4 (perceived symptoms). Walking distance decreased in half of the 53 patients measured posttreatment, but self-perceived change in exercise tolerance improved in 84% and was explained by change in walking distance, by less desaturation, and by less dyspnea ($R^2 = 0.55$, $p = 0.005$). Qualitative analysis showed that 29 of 53 patients improved in three or four factors. Performance in the 6MWT can be described with four statistically independent and clinically interpretable factors. Because clinically relevant changes consist of more than only walking distance, assessment of functional exercise tolerance in patients with COPD improves by reporting multiple variables.

Impairment of functional exercise tolerance (FET) is an important feature of chronic obstructive pulmonary disease (COPD). Physical deconditioning and impaired lung function are the main causes of decreased FET (1, 2). Self-pacing is suggested as another major contributor to performance in daily activities (3). An important treatment goal in pulmonary rehabilitation is improvement of FET by exercise training and training of self-pacing skills (1, 3). However, exercise training and training of self-pacing skills may have contradictory effects on outcome parameters for FET. FET is usually assessed by timed walking tests such as the 6- or 12-min walking test because of the relevance of walking to daily activities (2, 3). The usual measure of performance in the 6-min walking test (6MWT) is the walking distance. FET encloses more than walking distance and additional information on other aspects such as dyspnea, oxygen saturation, cardiovascular fitness, and walking technique is needed (3, 4). However, changes in these aspects of FET, which may be of equal importance for a patient, are seldom used to report results of walking tests (5, 6). In our opinion the effect of rehabilitation will be underestimated or misunderstood if the walking distance is the only outcome parameter for FET, especially in programs with attention for self-pacing skills. Performance in an exercise test should be described with multiple, responsive factors to give a more complete picture of (changes in) FET.

In several studies with patients with COPD the statistical method of factor analysis has been used to characterize the pathophysiological condition of COPD (7–10). Factor analysis is a data-reduction method that reduces multiple interrelated variables to a few clinical interpretable factors (11).

The first aim of our investigation was to describe baseline performance in the 6MWT with more factors than only walking distance. These factors were derived from multiple variables obtained from walking tests in patients with COPD. An exploratory factor analysis has been performed on physiological measurements, dyspnea ratings, and walking distance recorded during pretreatment 6-min walking testing. The second aim was to assess if the use of multiple factors adds to walking distance in describing change in performance after inpatient pulmonary rehabilitation (IPR). For this purpose, change in the composite factors and recorded variables was compared with self-perceived change in exercise tolerance. Change in health-related quality of life (HRQL) was recorded to assess the overall effectiviness of the IPR.

METHODS

Patients and Program

We studied patients with mild to severe COPD referred to the 2-wk diagnostic period preceding our 3- to 6-mo inpatient pulmonary rehabilitation program (IPR). The duration of the IPR depends on the specific problems and individually tailored treatment goals of a patient (*see* the online data supplement). The main reasons for referral were an unstable disease pattern and/or a high burden of disease, characterized by frequent hospitalization, high medication usage, and/or psychosocial problems. The inpatient program aims at optimizing functioning in daily life. The key components of the program are exercise training, optimizing the medication regimen, education, extensive psychosocial support, and training of self-management skills, including self-pacing. Based on previous experience and treatment goals, we expected a high variety in change in FET: patients who improve in one aspect of FET may have worse scores on other aspects.

Diagnosis was done according to ERS criteria (12) by the attending pulmonologist. All patients gave their informed consent. The study protocol was approved by the medical ethics committee.

Assessments

Eighty-three patients (*see* the online data supplement) were consecutively included in this study from March 1996 to December 1997 (including three younger patients having asthma with major irreversible airflow obstruction). Pretreatment assessments were done in the diagnostic period preceding the inpatient pulmonary rehabilitation program. Posttreatment data were collected in 53 (*see* the online data supplement) of 83 patients in the week prior to discharge. Lung function (*see* the online data supplement) values are expressed in %predicted (13). Self-reported dyspnea was assessed with the five-point MRC dyspnea scale (range 1–5) (14). Self-perceived change in exercise tolerance was assessed at discharge with a global rating of change ques-

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tion, using a five-point response scale (much worse, worse, the same, better, and much better). Change in HRQL was assessed with the Quality of Life for Respiratory Illness Questionnaire (QoLRIQ) (15).

Walking Test Protocol

The walking test protocol (*see* the online data supplement) was modified from Steele (3). No encouragement was given (16) so as not to interfere with self-pacing. Transcutaneous oxygen saturation (Sto_2) and heart rate were measured with a portable pulse oximeter (N20-PA; Nellcor Puritan Bennett, Pleasanton, CA). Perceived dyspnea and perceived effort were rated with the modified Borg scale (range 0–10) (17).

Statistical Analysis

Statistical analysis (*see* the online data supplement) included assessment of normality, summarizing baseline data, significance testing for change in factors and in HRQL domains, computation of standardized response means (SRM) for HRQL domains, rank correlation coefficients, and forward stepwise multiple regression analysis to assess predictors for change in walking distance.

An exploratory factor analysis (*see* the online data supplement) (11) was performed on variables recorded during the last baseline test and on derived variables describing increase, decrease, minimum, and maximum. Factor analysis is a data-reduction technique that consists of two steps: clustering of variables with shared variance, which yield factors, and then simplifying the factor structure by varimax rotation, which improves interpretability.

We selected one original variable for each factor, based on a high factor loading and clinical relevance (7). The pattern of change in these selected variables was qualitatively analyzed by dichotomizing change scores to improvement (larger walking distance, higher minimal saturation, less dyspnea, lower maximal heart rate) and deterioration.

RESULTS

Patient characteristics including anthropometric data, lung function variables, and MRC dyspnea score are presented in Table 1. Most variables, except for the saturation variables, were not normally distributed. Median and range of the variables used in the analysis are listed in Table 2. The minimal Sto_2 is lower than the preset stop criterion of 86%; this is caused by patients who continued to desaturate after stopping. There were no significant differences at baseline between the groups with and without posttreatment assessments. The principal components analysis yielded a five-factor structure explaining 85.7% of the variance in the data set. Because the fifth factor contained only one variable (dyspnea at 0 min) a four-factor structure was forced. This resulted in essentially the same factor structure, explaining 78.4% of the total variance, with the one variable of the fifth factor contributing to the fourth factor. The stability of the factor structure was checked by conducting additional factor analyses. The structure remained the same and the percentage explained variance and values and significance of the factor loadings did not appreciably change when excluding the six patients with mild COPD, by excluding the patients with asthma, by excluding the patients without posttreatment measurements, by using a different extraction method (maximum likelihood procedure), by use of other rotation procedures such as oblique rotation, or by using the mean values of the three baseline 6MWTs instead of the values of the last 6MWT.

The significant factor loadings of the four-factor solution after rotation are listed and grouped by factor in Table 3. The heart rate at 0, 6, + 2 min and maximal heart rate loaded significantly on factor 1. The walking distance, the heart rate increase while walking, and heart rate decrease in the recovery

TABLE 1. PATIENT CHARACTERISTICS

Parameter	Mean (SD)	Range
Sex		
Male	42	
Female	41	
Age, yr	60.4 (12.0)	26–82
Portable oxygen/walking aid*		
Both	20	
Only walking aid	8	
Only oxygen	1	
MRC score (range 1–5)	4.6 (0.7)	2–5
FEV_1, L	1.04 (0.45)	0.38–2.46
FEV_1, % predicted	36.9 (12.8)	15.0–70.0
FVC, % predicted	72.6 (19.7)	28.0–122.7
TLC, % predicted	116.7 (22.2)	70.0–166.9
RV, % predicted	185.8 (48.2)	110.9–311.0

Definition of abbreviations: FEV_1 = forced expiratory volume in 1 s; FEV_1 % pred = FEV_1 as percent of predicted value; FVC = forced vital capacity; MRC = Medical Research Council dyspnea score; RV = residual volume; TLC = total lung capacity.

* Walking aids: wheeled walker (26), walking stick (1), wheelchair (1).

TABLE 2. VARIABLES USED IN THE FACTOR ANALYSIS

Parameter	Median	Range
HR 0 min, bpm	92	61–133
HR 6 min, bpm	109	80–174
HR + 2 min, bpm	96	61–141
HR max, bpm	113	84–174
HR increase, bpm	15	−6–85
HR decrease + 2 min, bpm	−8	−50–18
Sto_2 0 min, %	95	90–100
Sto_2 6 min, %	91	84–100
Sto_2 minimum, %	93	83–99
Sto_2 decrease, %	−3	−12–1
Dyspnea 0 min (range 0–10)	3	0–5
Dyspnea 6 min (range 0–10)	4	0–8
Dyspnea increase	1	−1–6
Perceived effort (0–10)	3	0–10
6MWD, m	311	72–840

Definition of abbreviations: HR = heart rate; HR decrease + 2 min = heart rate decrease in 2-min recovery period; HR increase = heart rate increaxe during walking test; HR max = maximal observed heart rate; HR + 2 min = heart rate after 2-min recovery; Sto_2 = transcutaneous oxygen saturation; 6MWD = 6-min walking distance.

TABLE 3. SIGNIFICANT FACTOR LOADINGS AFTER ROTATION*

	Factor			
Parameter	1	2	3	4
HR 0 min	0.82	†		
HR 6 min	0.91			
HR + 2 min	0.88			
HR max	0.87			
HR increase		0.86		
HR decrease + 2 min		0.83		
6MWD		0.77		
Sto_2 0 min			0.66	
Sto_2 6 min			0.96	
Sto_2 minimum			0.99	
Sto_2 decrease			0.78	
Dyspnea 0 min				0.66
Dyspnea 6 min				0.97
Perceived effort				0.90
Dyspnea increase				0.69
Eigenvalue‡	3.16	2.78	3.04	2.80
Explained Variance, %	21.0	18.5	20.2	18.7

Definition of abbreviations: HR = heart rate; HR decrease + 2 min = heart rate decrease in 2-min recovery period; HR increase = heart rate increaxe during walking test; HR max = maximal observed heart rate; HR + 2 min = heart rate after 2-min recovery; Sto_2 = transcutaneous oxygen saturation; 6MWD = 6-min walking distance.

* Only significant factor loadings ($>$ 0.572) are listed.

† Nonsignificant factor loadings between 0.4 and 0.57.

‡ Recalculated eigenvalues after rotation are listed.

period loaded on factor 2. Sto_2 at 0 and 6 min, minimal Sto_2, and decrease in Sto_2 loaded on factor 3. Dyspnea at 0 and 6 min, increase in dyspnea, and the perceived effort loaded on factor 4. Heart rate at 0 min also had a moderate (> 0.4) but nonsignificant loading on factor 2. The equations for the composite variables are listed in Table 4. Using the values of the baseline test with the highest walking distance gave a small difference in the factor structure: heart rate at 6 min and maximal heart rate had also a significant loading (0.6) on factor 2, whereas the nonsignificant loading of heart rate at 0 min disappeared.

Analysis of the pre/posttreatment change in 53 patients was performed on both the composite variables and the selected variables (1 for each factor). The results of significance testing were similar for the composite and selected variables. For clarity only the results of the selected variables are presented. Only minimal Sto_2 showed a significant improvement (mean 90.4% to 91.8%, $p = 0.00008$, range −2% to +4%). Analysis of change in walking distance showed that 25 patients improved (median +54 m, range +1 to +178) and 28 patients walked less (median −46 m, range −4 to −159) (*see* Table E1 in the online data supplement). Dyspnea at 6 min changed in a similar way: 12 patients improved 2 or more points and 9 patients had a worse dyspnea score ($\geqslant 2$ points). Qualitive analysis showed that 29 of 53 patients improved in three or four variables and 7 patients deteriorated in three variables (*see* Table E2 in the online data supplement). Fifty patients reported self-perceived change in exercise tolerance (*see* Table E3 in the online data supplement): 42 reported improvement whereas 17 of the subjectively improved patients had decreased walking distance at discharge. The group of patients with an individualized treatment goal on improvement of exercise tolerance ($n = 17$) had a nonsignificant mean improvement of 10 m in walking distance, accompanied by significant improvements in minimal oxygen saturation during the walking test (92.8% to 94%, $p = 0.009$), perceived exertion (4.1 to 3.1, $p = 0.01$), and perceived dyspnea (4.1 to 3.1, $p = 0.01$).

Change in walking distance was significantly correlated with change in desaturation ($r = 0.43$, $p = 0.005$), with self-perceived change in exercise tolerance ($r = 0.56$, $p = 0.00002$), and with change in several HRQL domains: general activities, ADL functioning, social activities, total score ($r = 0.47, 0.36, 0.39, 0.41$, all $p < 0.05$) but not with change in maximal heart rate, change in dyspnea at 6 min, or initial walking distance. Only change in desaturation and self-perceived change in exercise tolerance remained significant predictors of change in walking distance in multiple regression analysis (adjusted $R^2 = 0.48$, $p = 0.001$). Multiple regression analysis on self-perceived change in exercise tolerance with other change variables as independent variables showed that self-perceived change is not only explained by change in walking distance ($R^2 = 0.31$, $p = 0.004$) but also by less desaturation (additional $R^2 = 0.12$, $p = 0.04$) and less dyspnea (additional $R^2 = 0.11$, $p = 0.04$) (total adjusted $R^2 = 0.55$, $p = 0.005$).

All domains from the QoLRIQ improved significantly (*see* Table 5). Most domains showed moderate ($SRM > 0.5$) to large ($SRM > 0.8$) clinically relevant changes, with general activities and ADL showing the largest absolute changes.

DISCUSSION

This study presented a new, more detailed approach of analyzing the 6MWT as a measure of performance for patients with COPD. Encouragement was omitted from the walking test protocol as not to interfere with self-pacing. Factor analysis of a set of variables with clinical relevance to FET yielded a stable four-factor structure. The use of multiple factors allowed a detailed assessment of change in FET: the major part of the patients improved in two or more factors; patients with an individualized treatment goal on improvement of exercise tolerance improved significantly in all factors except walking distance; and the improvement in self-perceived exercise tolerance was explained by walking distance, less desaturation, and less dyspnea, whereas the larger part of the patients showed a decrease in walking distance.

Factor Structure

Besides walking distance, measurements of physiological parameters and dyspnea ratings were obtained from 83 patients with mild to severe COPD. Factor analysis reduced the 15 selected variables to four factors explaining 78.4% of the total variance in the data set. Our clinical interpretation of the factors is as follows. Factor 1 contains the heart rate variables measured during testing. This factor describes the "heart rate pattern." Factor 2 is made up of the walking distance and the two dynamic heart rate variables: the increase while walking and the decrease in the recovery period. This factor is interpreted as "endurance capacity." The variables for oxygen (de)saturation belong to factor 3; this can be interpreted as "impairment of oxygen transport." Factor 4 contains the dyspnea and effort variables; this factor is named "perceived symptoms."

The factor score coefficients resulting from the factor analysis were used to compute a composite variable for each factor (*see* the online data supplement). Following the suggestion by Ries and coworkers (7), we selected for each factor the variable that represents most closely the conceptual meaning of the factor. This variable should be a valid outcome measure and combine a high factor loading with a clear clinical interpretation. We selected as follows: maximum heart rate for factor 1, walking distance for factor 2, minimal saturation for factor 3, and perceived dyspnea at 6 min for factor 4.

Change in FET

In this study we further assessed if the obtained factors added to walking distance in describing change in FET after treatment in 53 patients. Only minimal Sto_2 improved significantly. Despite the lack of significant change in the other selected variables, moderate to large, both positive and negative changes were seen. The qualitative analysis showed a high variation in the pattern of change: most patients improved in two or three variables but deteriorated in another variable.

TABLE 4. COMPUTATION OF COMPOSITE FACTOR VARIABLES

Factor Name	Equation Using Factor Score Coefficients
Heart rate pattern	0.27 × (HR 0 min) + 0.30 × (HR 6 min) + 0.29 × (HR + 2 min) + 0.29 × (HR-maximum)
Endurance capacity	0.28 × (6MWD) + 0.31 × (HR increase) + 0.30 × (HR decrease)
Impairment of oxygen transport	0.22 × (Sto_2 0′) + 0.32 × (Sto_2 6′) + 0.33 × (Sto_2 minimum) + 0.26 × (Sto_2 decrease)
Perceived symptoms	0.25 × (dyspnea 0 min) + 0.36 × (dyspnea 6 min) + 0.34 × (perceived effort) + 0.26 × (dyspnea increase)

Definition of abbreviations: HR = heart rate; HR decrease + 2 min = heart rate decrease in 2-min recovery period; HR increase = heart rate increaxe during walking test; HR max = maximal observed heart rate; HR + 2-min = heart rate after 2-min recovery; Sto_2 = transcutaneous oxygen saturation; 6MWD = 6-min walking distance.

TABLE 5. CHANGE IN HEALTH-RELATED QUALITY OF LIFE

Domain Name	Baseline Score*	Change Score*	p Value of Change	SRM†
Breathing problems	3.44	0.67	0.000003	0.77
Physical problems	3.38	0.67	0.000001	0.84
Emotions	3.22	0.67	0.000007	0.73
General activities	4.50	1.50	0.000001	0.95
Triggering situations	3.14	0.57	0.0004	0.56
Activities of daily life	5.14	1.00	0.00002	0.79
Social activities	4.43	0.57	0.02	0.43
QoLRIQ total	3.87	0.72	0.000001	0.94

Definition of abbreviations: QoLRIQ = Quality of Life for Respiratory Illness Questionnaire.
* Median score.
† SRM = change score divided by standard deviation of change score.

Although we neglected the magnitude of the changes, this analysis suggests that patients with a decreased walking distance are not necessarily deteriorated because they may have improved in other factors. This suggestion is supported by three findings in this study: all HRQL domains showed highly significant and clinically relevant improvement; patients with an individualized treatment goal on improvement of exercise tolerance improved significantly in all factors except walking distance; and the majority of the patients with decreased walking distance at discharge perceived an improved exercise tolerance. This last point was also found by Redelmeier and coworkers (18); their suggestion was that patients do not have perfect memory of their past functional status. We think that the difference between objective and subjective change is mainly explained by change in other factors related to FET. An advantage of our factor approach may be that in case of specific treatment goals, analysis of change may be focused on the factor related to that treatment goal, such as improvement of dyspnea or O_2 desaturation.

Factor Analysis in COPD

Factor analysis has previously been used in studies with patients with COPD (7–10). These studies selected several pathophysiological measurements and dyspnea assessments from clinical ratings and disease-specific HRQL measures in order to characterize the pathophysiological condition of COPD. In contrast to these studies we selected only variables from one specific exercise test (the 6MWT). We excluded variables related to FET that cannot be recorded during testing. In our study walking distance and dyspnea ratings belong to different factors, which suggests that they are different aspects of FET (3). In the study by Wegner and coworkers (9) walking distance and dyspnea ratings formed a factor together, apart from airway obstruction and pulmonary hyperinflation. In factor analysis studies without walking distance, all dyspnea measures fall into one factor (8, 10). The sample sizes of all studies using factor analysis in patients with COPD, including our own study, are smaller than recommended (11). Despite this the factor structures are stable, which may be explained by the use of homogeneous patient groups.

Limitations

This study has several limitations. We already mentioned the rather small but apparently adequate sample size. Our protocol for the walking test differed in several aspects from the protocol proposed by Steele (3), most noticeable in omitting standard phrases of encouragement. We had two reasons for not providing encouragement. The first is that we expected that the most severely impaired patients would need frequent resting during the walking test. We felt that an encouraging phrase while a patient is resting is unbecoming. The second reason is that training of self-pacing skills is an important treatment goal in our IPR program. Encouraging may interfere with acquired self-pacing skill. Because the effect of encouragement is large (about 30 m) (16), comparisons with the change in walking distance found in the literature must be made with caution. The threshold for clinical relevant change in walking distance of 54 m suggested by Redelmeier and coworkers (18) may not be valid using this modified protocol. A different approach to computing the size of clinically relevant change is the effect size (ES) (19). Using the baseline standard deviation of 152 m (this study), a small ES of 0.2 would be equal to a difference of 30.4 m.

Our study showed no overall improvement in 6-min walking distance. This is at variance with the results of most pulmonary rehabilitation programs, both outpatient and inpatient. This lack of significant change in walking distance may be partly explained by the absence of encouragement, partly by the focus on self-pacing skills (*see* the online data supplement), and partly by the variation in the individualized treatment goals.

Another limitation is that we did not include several variables associated with self-pacing that may improve the clinical interpretability and explained variance of the factor analysis. Alas, we recorded “time spent resting” and “frequency of resting” only in a small part of the study group.

Clinical Relevance

In our opinion, a multifactorial interpretation of the 6-min walking test will be of value in the estimation of clinical efficacy of rehabilitation programs and in the assessment of FET. The main advantage of using multiple factors (or variables) to describe performance is the possibility of assessing change in several aspects of FET simultaneously instead of only in one aspect, which is one of the disadvantages of the 6-min walking test (20). When assessing change in several variables simultaneously, a statistical and a clinical problem arises. The statistical problem is the increased type I error due to multiple testing (*see* the online data supplement), which can be controlled by applying a Bonferroni correction. The clinical problem is to judge the importance of the observed changes in all factors together. It will depend on the specific treatment goal for a patient and the size of the changes if the improvement in one factor outweighs the deterioration in another factor. This judgment may be aided by assessing the self-perceived change in exercise tolerance and the patient’s satisfaction with that change. Reviewing several aspects of FET simultaneously can be compared with analyzing a multidomain quality of life questionnaire. It is important to know if an overall improvement did occur, but it may be much more interesting to know which domains did improve and to analyze the pattern of improvement. Reporting multiple factors will be especially useful for (pulmonary) rehabilitation programs with attention for training of self-pacing skills as a method to prevent dyspnea and exhaustion: a decrease in walking distance may be accompanied with less desaturation and less dyspnea or perceived effort, as was shown in this study.

The clinical relevance of multiaspect reporting of FET lies both on a program and on a patient level. On a program level it is necessary to know if the observed change resembles the main treatment goals, if patients have improved in those areas that received most attention, and if patients that became worse on an outcome measure such as walking distance improved on other aspects of FET. This last argument is also important to individual patients. A decrease in walking distance may leave the patient disappointed about the treatment result and probably confused if the patient experienced a subjective improvement in FET. Reporting change in FET in more detail, while comparing with the expected treatment results, may clarify this confusion in patients.

Further Research

Several topics addressed in this study need further investigation. The magnitude of clinically relevant changes and valuing positive and negative changes simultaneously are basic questions for all situations with multiple outcome measures. Furthermore, the analysis of treatment effects with regard to the individual goals of a patient is essential for all treatment programs that employ individual adaptation of treatment based on the specific problems of the patient. Lastly, the factor structure found in this study should be confirmed in other patient samples, including both inpatients and outpatients with COPD.

Conclusion

To conclude, performance in 6-min walking testing can be described by four statistical independent and clinical interpretable factors: endurance capacity, heart rate pattern, perceived symptoms, and impairment of oxygen transport. Assessment of change in performance is improved by using selected variables representing these factors instead of merely walking distance. Reviewing change in all factors simultaneously may be useful both in clinical and in research settings.

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