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Relationship between dyspnoea, pulmonary function and exercise capacity in patients with cystic fibrosis

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The median age of survival in patients with cystic fibrosis (CF) has improved considerably. Despite this improvement, deterioration of pulmonary function and decrease in exercise capacity are still the main problems for many patients. Although dyspnoea is a common complaint in CF patients, relatively little regard has been paid to this symptom. This study examined the relationship between dyspnoea, bicycle exercise capacity and pulmonary function in patients with CF.

In 14 patients in a stable clinical condition, pulmonary function [forced expiratory volume in 1 s (FEV_1), inspiratory vital capacity (IVC)], bicycle exercise capacity [maximum exercise capacity (Wmax)], subjective degree of dyspnoea during daily living [Medical Research Council (MRC) dyspnoea scale], and during exercise (Borg scale) were assessed.

The mean (SD) age of the patients was 25 (6·8) years, FEV_1 was 41 (19)% predicted, IVC was 63 (17)% predicted and FEV_1/IVC ratio was 47 (10)%; median (range) Wmax was 55 (0–79)% predicted. Bicycle exercise test performance appeared to be mainly determined by pulmonary function and MRC dyspnoea grade; multiple regression equation containing FEV_1 and dyspnoea accounted for 76% of the variance in Wmax (% predicted) ($W\text{max} = -7{\cdot}9\,\text{dysp} + 1{\cdot}1 FEV_1, +24$). Exercise dyspnoea, assessed by the Borg scale, showed a significant linear correlation with minute ventilation. ($\dot{V}_E$), maximal voluntary ventilation (MVV) (%) (r=0·76; P<0·001). Medical Research Council dyspnoea score correlated relatively poorly with FEV_1 (% predicted) ($r = -0{\cdot}17$; n.s.) and IVC (% predicted) ($r = -0{\cdot}48$; n.s.). Borg score at maximal exercise did not correlate with MRC dyspnoea score ($r = -0{\cdot}07$). $Borg_{50\%}$ score correlated significantly with MRC dyspnoea score (r=0·61; P<0·05).

These results show that dyspnoea has an influence on exercise capacity. Dyspnoea score showed a large inter-individual variation, not strongly related to pulmonary function. It is concluded that dyspnoea deserves more attention in CF patients and needs to be assessed in rehabilitation programmes and other intervention studies in these patients.

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Introduction

In patients with cystic fibrosis (CF), the median age of survival has improved considerably (1). Despite this increase in expected life years, a progressive decrease in exercise capacity is still a major problem for many patients. Limitation in exercise capacity has been ascribed to deterioration in pulmonary function leading to a decreased ventilatory capacity, and also to malnutrition, which leads to a loss in muscle strength (2–6). Effects of exercise rehabilitation programmes have traditionally been evaluated by exercise capacity and pulmonary function (3,7,8). In contrast to patients with chronic obstructive pulmonary disease (COPD), where

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recent research has focused on the impact of the disease on patients' disability such as dyspnoea and exercise tolerance (9–12), little attention is paid to this subject in CF patients. In COPD patients, the substantial impact of dyspnoea on patients' quality of life has been reported in several studies (9,11,13,14). Dyspnoea, and therefore fear of dyspnoea during activity, seems to play an important role in physical deconditioning in COPD patients (15,16). Dyspnoea may lead to avoidance of activity and patients run into a debilitative cycle (17,18). Mahler *et al.* (9) reported that measurement of dyspnoea can be useful in the evaluation and care of patients with other chronic disease.

The purpose of the present study was to examine the relationships between dyspnoea, exercise capacity and pulmonary function in patients with CF.

Patients and Methods

PATIENTS

Fourteen patients with CF, referred for a routine ergometry test, were asked to participate in this study. No patients refused to participate. All patients were older than 16 years and had recurrent respiratory tract infections and persistent cough. All patients provided written informed consent. The study was approved by the Medical Ethics Committee of the University Hospital.

METHODS

Exercise capacity, pulmonary function and dyspnoea were assessed in each patient during a clinically stable period. Inspiratory vital capacity (IVC) and forced expiratory volume in 1 s (FEV_1) were measured using a water-sealed spirometer (Lode). Predicted values of Quanjer were used to express pulmonary function % predicted values (19). Maximal voluntary ventilation (MVV) was calculated from $35 \times FEV_1$.

Exercise tolerance was assessed using an automatic bicycle ergometry equipment (Jaeger EOS sprint) during continuous ECG recording. Each subject exercised continuously (pedal speed: 60 rpm) with an initial work load of 0 W, which was increased every 3 min by 20 W. Heart rate (HR), breathing frequency (BF), minute ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured continuously. The test was terminated by the patient's symptoms or, if necessary, at the physician's discretion (i.e. decline in blood pressure, ECG changes, attainment of a given heart rate) (20). The maximal work load was defined as the highest load which could be reached and maintained for at least 1·5 min. Maximum exercise capacity (Wmax) expressed as the percentage of the predicted maximum exercise capacity using the equation of Wasserman *et al.* (21) was used for analysis.

Before exercise and during the last 10 s of each work level, patients were asked to rate the subjective degree of dyspnoea using the modified Borg scale (22). This category scale is an indicator of the intensity of dyspnoea. The scale ranges from 0 to 10 where a value of 0 represents 'nothing at all' and a value of 10 denotes that the intensity of dyspnoea is maximal. The Borg scale shown to patients was printed on a sheet of paper after a standard set of instructions (16). Borg scores at work levels representing 25% ($Borg_{25\%}$) and 50% ($Borg_{50\%}$) of maximal work load, and maximal Borg scores ($Borg_{max}$) were used for statistical analysis.

Moreover, the Dutch version of the Medical Research Council (MRC) dyspnoea scale was used to rate limitation in function due to dyspnoea (23) (Table 1). This scale is based on six grades with regard to dyspnoea during various physical activities and during rest. To grade dyspnoea with the MRC scale, patients were interviewed by asking questions concerning the patient's symptoms according to the instructions reported by Van der Lende *et al.* (24). A higher MRC grade indicates more impairment due to dyspnoea.

Statistical analysis was performed using the 'Statistical Package for the Social Sciences' (SPSS-Pc$^+$) (25). Distribution of the variables was tested using the Kolmogorov–Smirnov Goodness of Fit test. Data were not significantly different from the normal distribution. Pearson's r-test was used to examine the relation of pulmonary function and exercise capacity. Spearman's rank-order correlation coefficients were determined between ordinal dyspnoea ratings and physiological parameters. Stepwise multiple regression analysis with all physiologic variables and dyspnoea scores was performed to build a model to predict maximum exercise capacity. A P value <0.05 was considered statistically significant.

TABLE 1. Dutch version of the Medical Research Council dyspnoea scale

Grade	Description
No=1 Yes=continue	Are you troubled with breathlessness when hurrying on the level, walking up a slight hill, or going upstairs at normal pace?
No=2 Yes=continue	Are you troubled with breathlessness when walking with people of the same age at normal pace on the level?
No=3 Yes=continue	Do you have to stop for breath when walking at own pace on the level?
No=4 Yes=continue	Do you become short of breath at rest?
Sometimes=5 All the time=6	Sometimes or all the time?

Results

Anthropometric data, pulmonary function, exercise capacity and MRC dyspnoea grade are presented in Table 2. These results represent a spectrum from mild to severe CF based on pulmonary function data. Mean *W*max of the group was 48% predicted, but a wide range of values was noted. The latter was partly based on the fact that two patients were unable to perform the bicycle exercise test (*W*max: 0% predicted). These patients demonstrated severe hypoxaemia at rest (SaO_2 less than 80%). During the exercise tests, the 12 other patients were considered to perform maximally according to usual criteria (20,26).

TABLE 2. Anthropometric data, pulmonary function, exercise capacity and dyspnoea score of the cystic fibrosis patients in this study

n=14	Mean (SD)	Range
M/F	10/4	
Age (years)	25 (6·8)	16–40
Height (cm)	175 (7)	164–187
Weight (kg)	59 (6)	49–71
FEV_1 (l)	1·49 (0·68)	0·61–2·85
FEV_1 (% predicted)	41 (19)	20–79
IVC (l)	3·13 (1·01)	1·45–4·58
IVC (% predicted)	63 (17)	33–90
FEV_1/IVC (%)	47 (10)	26–69
MRC dyspnoea	2·5 (1·3)	1–5
*W*max (% predicted)	48 (28)	0–79
Maximal Borg score (*n*=12)	6 (2)	3–10

FEV_1, forced expiratory volume in 1 s; FEV_1 (% predicted), FEV_1 as a percentage of the predicted value; IVC, inspiratory vital capacity; IVC (% predicted), IVC as a percentage of the predicted value; FEV_1/IVC (%), FEV_1 as a percentage of IVC; *W*max (% predicted), maximal exercise capacity as a percentage of the predicted value; MRC dyspnoea, Medical Research Council dyspnoea scale; Maximal Borg score, Borg score at maximum work load.

FEV_1 (% predicted (Fig. 1) and IVC (% predicted) showed a significant comparable correlation with exercise capacity (r=0·79 and 0·77, respectively; P<0·001).

Medical Research Council dyspnoea score was not significantly related to FEV_1 (% predicted)

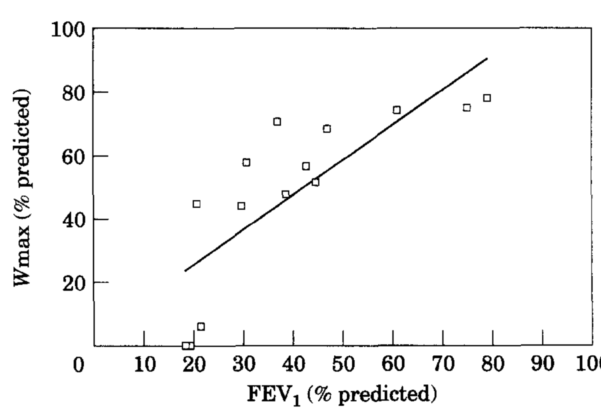

FIG. 1. Relationship between FEV_1 (% predicted) and maximal exercise capacity (*W*max, % predicted). Pearson's r correlation coefficient is 0·79; P<0·001.

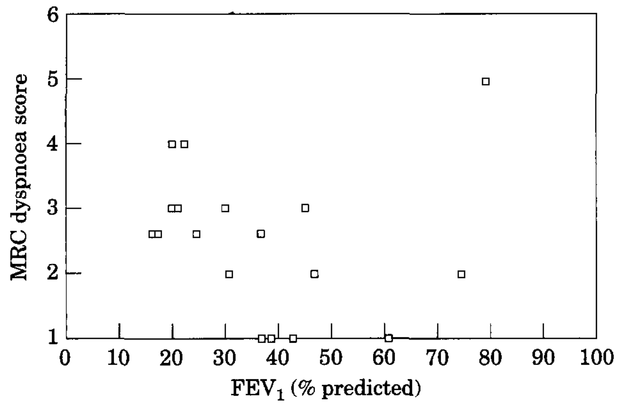

FIG. 2. Relationship between FEV_1 (% predicted) and Medical Research Council dyspnoea score. Spearman's *r* correlation coefficient is $-0{\cdot}17$ (n.s.).

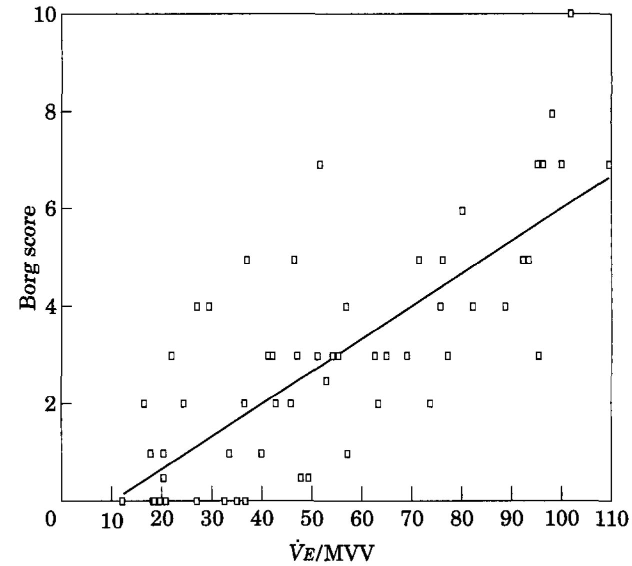

FIG. 3. Relationship between minute ventilation ($\dot{V}$E)/maximal voluntary ventilation (MVV) (%) and Borg score. Spearman's *r* correlation coefficient is 0·76; $P<0{\cdot}001$.

($r=-0{\cdot}17$; n.s.) and IVC (% predicted) ($r=-0{\cdot}48$; n.s.). It should be noted that one of the patients showed an extremely high MRC dyspnoea score in comparison to good pulmonary function (Fig. 2).

The stepwise multiple regression equation indicated that FEV_1 and MRC dyspnoea score accounted for 76% of the variance in *W*max (*W*max$=-7{\cdot}9$dysp$+1{\cdot}1FEV_1+24$). FEV_1 was the dominant determining factor, but MRC dyspnoea score contributed significantly to the model, increasing the explained variance in *W*max from 62 to 76%.

Exercise dyspnoea, assessed by the Borg scale on each work level in 12 patients, showed a significant linear correlation with $\dot{V}$E as a percentage of MVV [$\dot{V}$E/MVV(%)] ($r=0{\cdot}76$; $P<0{\cdot}001$) (Fig. 3). Medical Research Council dyspnoea score correlated significantly with $\dot{V}$E/MVV (%) at rest ($r=0{\cdot}61$; $P<0{\cdot}05$). $Borg_{max}$ score and $Borg_{25\%}$ score were not significantly correlated to MRC dyspnoea score ($r=-0{\cdot}07$ and $r=0{\cdot}50$, respectively), and $Borg_{50\%}$ score correlated significantly with MRC dyspnoea score ($r=0{\cdot}61$; $P<0{\cdot}05$).

Discussion

The present study investigated the relationship between dyspnoea scores, pulmonary function tests and exercise capacity in patients with CF. The patient group in this study showed a broad range in pulmonary function, exercise capacity data and dyspnoea scores. This study shows a good correlation between pulmonary function and exercise capacity. Medical Research Council dyspnoea score correlates relatively poorly with pulmonary function, but contributes significantly to the prediction of exercise capacity. Furthermore, exercise dyspnoea, assessed by the Borg scale, was closely related to the level of ventilation as expressed by $\dot{V}$E/MVV ratio. Medical Research Council dyspnoea score was significantly related to $Borg_{50\%}$ score.

Good correlations between exercise capacity and the degree of airway obstruction in CF patients have been reported by several other authors (2–6), suggesting a relationship between ventilatory capacity and limitation in exercise. This is supported by the present authors' observation of a ventilatory limitation to exercise in nine of the 12 patients who performed the bicycle test. In these patients, $\dot{V}$E at maximal exercise was at least 89% of MVV, whereas healthy adults only utilize 70% of their MVV during exercise (4), indicating that a ventilatory limit had been reached.

Dyspnoea during daily living, as assessed by the MRC dyspnoea scale, and the perceived dyspnoea during the exercise test, assessed by the Borg scale on each work level, were related to the ventilation intensity as expressed by $\dot{V}$E/MVV ratio. This finding is consistent with the results of other studies in patients with COPD (15,27). These results suggest that perceived dyspnoea intensifies as ventilation increases in relation to maximum breathing capacity. At higher levels of ventilation, more work must be performed by the inspiratory muscles and this probably contributes to development of dyspnoea (28,29).

The present study found that in CF patients, pulmonary function values did not correlate significantly with limitation in function due to dyspnoea, as assessed by the MRC dyspnoea scale. It should be noted that the lack of a significant correlation between these parameters might be due to lack of statistical power. The number of CF patients studied (14 patients) might be too small to reveal statistically significant differences. In addition, it should be noted that one of the patients showed an extremely high MRC dyspnoea score in comparison to good pulmonary function. Statistical analysis without this outlier showed a significant relationship between FEV_1 (% predicted) and MRC dyspnoea score ($r=-0{\cdot}58$; $P=0{\cdot}035$). Previous data in patients with COPD regarding the correlation between pulmonary function and MRC dyspnoea score reveal contradictory results. Mahler *et al.* (9,10) showed that the clinical rating of dyspnoea was significantly related to results of pulmonary function tests, illustrating their common clinical observation that patients with reduced pulmonary function experience more dyspnoea. On the other hand, the reported moderate association between pulmonary function and MRC scores (r values about 0·45) implies a small explained variance in pulmonary function due to dyspnoea (about 16%). Jones considered the correlations between spirometry results and dyspnoea measures as weak in patients with chronic diseases of the airways (11). According to this, in COPD patients as well as in CF patients, limitation in function due to dyspnoea is not strongly related to severity of airway obstruction. This variability between individuals in the perception of dyspnoea is possibly related to psychologic factors. Illness behaviour of the patients could be an intermediating, but important, factor between pathophysiological processes, measured by spirometry and perceived dyspnoea during physical activity. The ascribed high score of MRC dyspnoea in comparison to good pulmonary function in one patient could be considered as an extreme example of this individual perception of dyspnoea.

Maximal Borg score and MRC dyspnoea score were not significantly correlated. This can be explained by the fact that MRC dyspnoea score and maximal Borg score provide different information about the problem of dyspnoea. The MRC dyspnoea scale is a clinical rating scale used to measure the impact of dyspnoea on various components of daily living, and therefore does not address situations of maximal exercise. The authors hypothesized that low to moderate work loads might be comparable to the level of daily physical activities as earlier suggested by Marcotte *et al.* (2). Dyspnoea scores at low to moderate work loads might therefore be comparable to dyspnoea scores during daily living. Therefore, the present study compared Borg scores at work levels representing 25% ($Borg_{25\%}$) and 50% ($Borg_{50\%}$) of maximal work load with MRC dyspnoea score. The described correlation between $Borg_{50\%}$ score and MRC dyspnoea score confirms this hypothesis.

Pulmonary function accounted for the greatest proportion of variance in exercise capacity. Independent of this effect of pulmonary function, MRC dyspnoea grade had a significant effect on exercise capacity. This is in agreement with studies in COPD patients, where the relation between clinical dyspnoea scores and exercise performance has also been shown to be good (11,30).

In conclusion, this study shows that dyspnoea has an influence on exercise performance. Dyspnoea score showed a large inter-individual variation, not strongly related to pulmonary function. Additional studies should focus on the influence of reduction of dyspnoea on exercise capacity. Dyspnoea scores should be used as an outcome parameter, in addition to exercise capacity, pulmonary function and quality of life, to evaluate the effect of exercise training in patients with CF.

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