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Relationship between subjective fatigue and physiological variables in patients with chronic obstructive pulmonary disease

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Patients with chronic illnesses, such as chronic obstructive pulmonary disease (COPD), report an increase in the perception of fatigue in the clinical setting. Subjective fatigue associated with physiological factors has not been reported. The purpose of this study was to determine the relationship between subjective fatigue and pulmonary function, respiratory and peripheral muscle force and exercise capacity in patients with COPD. Nineteen patients with COPD participated in the study [mean (SD) FEV_1 38% (17%) predicted]. Fatigue was measured with the Multidimensional Fatigue Inventory 20 (MFI-20) that includes the following subscale dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. The following physical variables were measured: forced expiratory volume in 1 s (FEV_1), vital capacity (VC), maximal inspiratory peak pressure (P_{Imax}), symptom-limited bicycle exercise capacity (maximum workload) and maximal voluntary isometric muscle force of both left and right quadriceps (Qu), hamstrings (Ha), biceps (Bi) and triceps (Tr).

The MFI-20 fatigue dimensions, reduced activity and reduced Motivation, are significantly correlated with FEV_1 (% predicted) ($r = -0{\cdot}62$, $r = -0{\cdot}55$ respectively). No significant correlation was found between the dimensions of fatigue and maximum workload. In contrast the fatigue dimension, physical fatigue, shows significant correlations with seven of eight muscle forces measured (Qu left $r - = 0{\cdot}49$, right $r = -0{\cdot}54$; Ha left $r = -0{\cdot}49$, right $r - 0{\cdot}38$; Tr left $r = -0{\cdot}61$, right $r = -0{\cdot}45$; Bi left $r = -0{\cdot}46$, right $r = -0{\cdot}48$). Data from this study show that activity and physical dimensions of subjective fatigue are related to pulmonary function and skeletal muscle force in COPD patients. Interventions to improve skeletal muscle force might improve subjective fatigue in patients with COPD.

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Introduction

Subjective fatigue is a very common symptom reported by patients, especially those with chronic diseases, in the clinical setting. It is known that fatigue can have negative influences on the condition and functioning of patients. The prevalence of subjective fatigue is estimated to range from 4% to 9% of all physician office visits in the United States and Canada (1). Despite this high prevalence of subjective fatigue, it remains a poorly understood symptom (2). There is little consensus about the definition of fatigue and the critical dimensions contributing to its perception. In the classification of nursing diagnosis, subjective fatigue is defined as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work (3). This definition implies that subjective fatigue is a multi-dimensional phenomenon including dimensions of activity and physical capacity to perform work.

Patients with chronic obstructive pulmonary disease (COPD) often report subjective fatigue. The relationship between quality of life and physiological variables in COPD patients has been investigated (4–9). A well-known instrument to measure quality of life in COPD is the Chronic Respiratory Disease Questionnaire (8). This questionnaire contains a dimension fatigue. Fatigue is in this case considered as one dimension. Physiological factors contributing to the perception of fatigue in COPD patients have not been reported. Fatigue in COPD is associated with the severity of pulmonary function and respiratory muscle

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TABLE 1. Characteristics of the patients

	Mean (SD)
Gender, m:f	16:3
Age (years)	64 (6)
FEV_1 (% predicted)	38 (17)
FEV_1 (% VC)	46 (14)
Reversibility (% predicted FEV_1)	4 (3)
P_{Imax} (cmH_2O; kPa)	82 (31); 8 (3)
Maximum workload (W)	78 (45)
BMI ($kg\,m^{-2}$)	24 (4)

FEV_1 (% predicted), forced expiratory volume in 1 s expressed as a percentage of the predicted value (10); FEV_1 (% VC), FEV_1 expressed as a percentage of the vital capacity; reversibility (% predicted FEV_1), reversibility expressed as a percentage of predicted FEV_1; P_{Imax} (cmH_2O), peak inspiratory mouth pressure; maximum workload (W), maximal exercise capacity on a bicycle ergometer; BMI, body mass index (weight height^{-2}).

impairment, which are both reduced in patients with COPD (10). Exercise capacity is also impaired in COPD. Maximal exercise capacity is often limited by subjective sensations, such as muscle fatigue prior to physiological limitations (11). The relationship between subjective fatigue and exercise capacity in COPD has not been reported. It has been shown that peripheral skeletal muscle force in patients with COPD is lower than that observed in healthy subjects (12). Roland and Ladegaard-Pederson indicated that weaker muscles require greater use of the present muscle mass to perform a given task, in association with an increased sensation of effort (13). It is possible that this mechanism is present in patients with COPD and contributes to the sensation of fatigue.

The purpose of this study was to determine the relationship between subjective fatigue and pulmonary function, peripheral muscle force and maximal exercise capacity in patients with COPD.

Patients and Methods

PATIENTS

Nineteen patients with COPD according to ATS criteria (14) participated in this study. Inclusion criteria were: age>45 years, FEV_1 (% predicted) <80%, reversibility <10% (percentage/predicted FEV_1), smoker or ex-smoker with a minimal of 5 pack-years. All patients were in a stable condition: there was no recent change in medication or symptoms, patients used only maintenance medication. No patients were on LTOT. Patients with signs suggestive for ischaemic heart disease, musculoskeletal disorders or other disabling diseases were excluded prior to participation in this study. The characteristics of the patients are summarized in Table 1. The study was approved by the Medical Ethics Committee of the University Hospital Groningen. All patients gave their written informed consent.

METHODS

Subjective Fatigue

Several fatigue questionnaires are used in order to quantify the degree of fatigue experienced. Most questionnaires are, however, lengthy and subjects who suffer from fatigue may have difficulties in filling in the questionnaire. Thereby often one-dimensional fatigue questionnaires are used, or fatigue is included as a one-dimensional concept in health-related quality of life questionnaires as in case of the CRQ. A major disadvantage of one-dimensional fatigue questionnaires is that they only quantify the overall fatigue but do not take into account differences in fatigue experience. For instance, some subjects may report fatigue as physical fatigue while others report fatigue as mental fatigue. The overall score may be the same but the fatigue experienced is very different. Based on these disadvantages the Fatigue Index 20 (MFI-20) was developed by Smets *et al.* (15,16) and used in our study. The psychometric properties of the MFI-20 are evaluated in cancer patients, patients with chronic fatigue syndrome, psychology students, medical students, army recruits and junior physicians (16). The MFI-20 has an established construct and convergent validity and shows good internal consistency in both the Dutch and English languages. The MFI-20 contains 20 positively and negatively directed statements which deal with 5 dimensions of fatigue, four statements per dimension:

- general fatigue, referring to the general functioning of the subject, with statements such as 'I feel tired';
- physical fatigue, somatic sensations directly referring to tiredness, for instance 'Physically I feel only able to do little';
- reduced activity, a potential consequence of subjective fatigue, such as 'I think I do very little in a day';
- reduced motivation, reflecting the motivation to start any activity, such as 'I dread having to do things';
- mental fatigue, referring to cognitive symptoms such as having difficulty in concentration, for instance 'It takes a lot of effort to concentrate on things'.

Patients are asked to rate their condition according to the most recent days. Each answer consists of an ordinal scale ranging from 'yes, that's correct' (score 1) to 'no, that's incorrect' (score 5). Scores range from 1 to 5. A higher score implies more severe fatigue. A score for each dimension is calculated by summation of the scores for each question per dimension. This score has a minimum of 4 and a maximum of 20. Thus a higher score implies more severe subjective fatigue. Mean (SD) values from a random sample of 139 subjects from the general population are as follows: general fatigue 9·9 (5·2), physical fatigue 8·8 (4·9), reduced activity 8·7 (4·6), reduced motivation 8·2 (4·0) and mental fatigue 8·3 (4·8) (unpublished data of Smets *et al.*).

Pulmonary Function

Forced expiratory volume in 1 s (FEV_1) and vital capacity (VC) were measured (Master screen Pneumo, Jaeger, Germany) and expressed as a percentage of predicted values derived from the European Community for Coal and Steel (ECCS) (17). Airway reversibility was assessed by measuring FEV_1 before and after inhalation of 40 μg of ipratropium bromide and was expressed as % pred. FEV_1. Maximal peak inspiratory pressure (PImax), a lung function measurement which is considered to be related to respiratory muscle strength, was measured at the mouth (18) using a water-sealed spirometer (Lode, Groningen, The Netherlands) and an X–Y recorder (Philips, Eindhoven, The Netherlands). All patients were in a seated position and wore a noseclip. The manoeuvre was carried out through an oval flanged mouthpiece. PImax was measured from residual volume (RV) against a closed shutter with a leak of 2·0 mm diameter to prevent the use of the buccinator muscles. PImax was assessed at least five times with 20–30 s rest between each pair of measurements. Normal values for the age group 55–64 years are for males 11 (3·3) kPa and females 8·8 (2·7) kPa and for the age group 65–74 years for males 8·7 (2·4) kPa and for females 8·2 (2·1) kPa (18). The mean values of the three highest scores were taken for analysis.

Exercise Capacity

All patients performed a symptom-limited bicycle exercise test. The initial workload during the exercise test was 0 W with a pedal speed of 60 cycles min^{-1}; the workload was increased every minute by 10 W. During each test electrocardiogram (ECG) (Hewlett Packard 7834A, Germany) and oxygen saturation (SaO_2) (Ohmeda Biox pulse oximeter 3740, Ohmeda, Louiseville, U.S.A.) were recorded. Criteria for ending the exercise test were intolerable symptoms levels, subjective inability to continue the test, ECG changes or reaching the maximal predicted heart rate (19). Sensations of dyspnoea and muscle fatigue at the maximal workload were quantified using the CR-10 Borg scale (20). This scale is widely used to quantify levels of dyspnoea but also sense of effort or fatigue (21). With this category scale the patient is able to quantify his or her degree of dyspnoea and muscle fatigue by a number from 0 to 10 (0, no dyspnoea or muscle fatigue at all; 10, maximal dyspnoea or muscle fatigue). The highest workload that could be maintained for one full minute was taken as the maximal work load.

Peripheral Muscle Force

Maximal voluntary isometric muscle force of the following muscles of the right and left extremity was measured using a hand held dynamometer [Force Evaluating & Testing (FET), Hoggan Health Industries Inc, U.S.A.]: quadriceps (Qu), hamstrings (Ha), triceps (Tr) and biceps (Bi). The force of the quadriceps and the hamstrings was measured while the patient was in a sitting position with the knee in 90° flexion. For the quadriceps measurement, the dynamometer was positioned at the ventral side just proximal of the ankle. The patient was asked to extend his or her knee as hard as possible. For the hamstrings measurement, the dynamometer was positioned at the dorsal side on the calcaneus. The patient was asked to bend his or her knee as hard as possible. The distance from the knee joint space to the location of the dynamometer was measured. The force of the triceps and biceps muscle was measured while the patient was in a supine position. The upper arm rested horizontally with the elbow in a 90° vertical position. For the biceps measurement the dynamometer was placed on the ventral side just proximal to the wrist joint, and for the triceps on the dorsal side. Biceps force measurement required the patient to bend the elbow as hard as possible; to measure the triceps force, the patient was asked to extend the elbow as hard as possible. The distance between the radiohumeral joint space and the position of the dynamometer was measured. For all measurements the break method was used. To employ this technique, the examiner gradually overcomes the force produced by the patient until the extremity gives away (22). All measurements were performed at least three times with recovery intervals of at least 10 s. In order to correct for differences in length of the extremity peak torques (N m) were calculated by multiplying the peak force in newtons with the distance of the dynamometer position to the proximal joint in metres. Peak torques were used in all analyses. Mean values of three technically correct measurements for each muscle were taken for analysis.

Nutritional Status

The nutritional status was estimated using the body mass index (BMI) (kg m^{-2}).

Statistical Analysis

Distribution of all variables was tested using the Kolmogorov–Smirnov goodness-of-fit test. Distribution of the variables did not significantly differ from a normal distribution. Correlation between pulmonary function variables, muscle force and maximum workload on the one hand and fatigue on the other hand was investigated by means of the Pearson correlation coefficient (r). The significance level was set at 5%. Physical variables that showed a significant correlation with fatigue were used as independent variables, and dimensions of fatigue were used as dependent variables in multiple regression analyses. All regression equations were generated by stepwise multiple regression analysis.

Results

SUBJECTIVE FATIGUE

Mean (SD) MFI-20 scores are as follows: general fatigue 13·9 (4·1), physical fatigue 13·9 (4·8), reduced activity 14·6 (3·1), reduced motivation 11·5 (4·4) and mental fatigue 9·7 (3·2). Compared with mean MFI-20 values in normal

TABLE 2. Pearson's correlation coefficients between subjective fatigue and pulmonary and respiratory muscle function, and *P* values

	FEV_1	*P*Imax
MFI-20		
General fatigue	− 0·28	0·20
	P=0·25	*P*=0·42
Physical fatigue	− 0·37	− 0·11
	P=0·12	*P*=0·67
Reduction activity	**− 0·62**	0·25
	P=0·01	*P*=0·31
Reduction motivation	**− 0·55**	0·14
	P=0·02	*P*=0·55
Mental fatigue	− 0·23	− 0·31
	P=0·35	*P*=0·20

TABLE 3. Pearson's correlation coefficients between subjective fatigue, exercise capacity, and Borg muscle fatigue and dyspnoea at maximal work load, and *P* values

	Maximum workload	Borg muscle fatigue	Borg dyspnoea
MFI-20			
General fatigue	− 0·28	− 0·16	− 0·39
	P=0·261	*P*=0·531	*P*=0·117
Physical fatigue	− 0·44	− 0·29	− 0·29
	P=0·064	*P*=0·253	*P*=0·249
Reduction activity	− 0·21	− 0·24	− 0·34
	P=0·398	*P*=0·349	*P*=0·176
Reduction motivation	− 0·39	**− 0·59**	**− 0·65**
	P=0·110	*P*=0·012	*P*=0·004
Mental fatigue	− 0·35	− 0·28	− 0·30
	P=0·159	*P*=0·268	*P*=0·244

TABLE 4. Mean muscle torques (N m) of the left and right quadriceps, hamstrings, triceps and biceps muscles

	Mean (SD) muscle torque (N m)
M. quadriceps left	95 (28)
M. hamstrings left	75 (22)
M. quadriceps right	93 (24)
M. hamstrings right	76 (22)
M. triceps left	43 (12)
M. biceps left	59 (16)
M. triceps right	45 (12)
M. biceps right	63 (17)

subjects, COPD patients in this study show higher mean scores of the MFI-20, suggesting that our patients suffer more from fatigue than normal subjects.

RELATIONSHIP BETWEEN SUBJECTIVE FATIGUE AND PHYSIOLOGICAL VARIABLES

The MFI-20 dimensions reduced activity and reduced motivation are significantly correlated with FEV_1 (% predicted). In contrast, no dimension of the MFI-20 is correlated with FEV_1/VC. Furthermore, MFI-20 dimensions do not correlate with *P*Imax (Table 2).

MFI-20 dimensions are not significantly correlated with maximum workload. The MFI-20 dimension reduced motivation is significantly correlated with Borg dyspnoea and fatigue scores at maximal workloads (Table 3).

Mean (SD) muscle forces are shown in Table 4. Physical fatigue is significantly correlated with almost all muscle forces (Table 5). Mental fatigue is also significantly correlated with the muscle force of the left biceps. This last correlation is considered to be a type I error. Furthermore, no other MFI-20 dimensions show a significant correlation with the muscle forces.

TABLE 5. Pearson's correlation coefficients between subjective fatigue and muscle torque and *P* values

	Quadriceps left	Hamstrings left	Quadriceps right	Hamstrings right	Triceps left	Biceps left	Triceps right	Biceps right
MFI-20								
General fatigue	− 0·43	− 0·41	− 0·39	− 0·32	− 0·25	− 0·34	− 0·13	− 0·25
	P=0·07	*P*=0·08	*P*=0·10	*P*=0·18	*P*=0·31	*P*=0·16	*P*=0·61	*P*=0·30
Physical fatigue	**− 0·49**	**− 0·49**	**− 0·54**	− 0·38	**− 0·61**	**− 0·46**	**− 0·45**	**− 0·48**
	P=0·03	*P*=0·04	*P*=0·02	*P*=0·11	*P*=0·01	*P*=0·05	*P*=0·05	*P*=0·04
Reduction activity	− 0·15	0·00	− 0·18	0·08	− 0·31	− 0·09	− 0·21	− 0·16
	P=0·53	*P*=0·99	*P*=0·47	*P*=0·74	*P*=0·19	*P*=0·72	*P*=0·38	*P*=0·52
Reduction motivation	− 0·34	− 0·25	− 0·33	− 0·18	− 0·18	− 0·24	− 0·05	− 0·21
	P=0·15	*P*=0·30	*P*=0·16	*P*=0·46	*P*=0·46	*P*=0·32	*P*=0·85	*P*=0·40
Mental fatigue	− 0·40	− 0·32	− 0·39	− 0·45	− 0·43	**− 0·47**	− 0·38	− 0·42
	P=0·09	*P*=0·18	*P*=0·10	*P*=0·06	*P*=0·07	*P*=0·04	*P*=0·11	*P*=0·07

TABLE 6. Pearson's correlation coefficients between muscle torques, maximal exercise capacity, BMI and Borg fatigue at maximal workload, and P values

	Maximum workload	BMI	Borg fatigue
M. Quadriceps left	**0·62**	**0·65**	**0·58**
	P=0·006	P=0·002	P=0·013
M. Hamstrings left	**0·69**	**0·56**	**0·43**
	P=0·001	P=0·012	P=0·083
M. quadriceps right	**0·58**	**0·56**	**0·66**
	P=0·011	P=0·014	P=0·004
M. hamstrings right	**0·66**	**0·59**	**0·48**
	P=0·003	P=0·007	P=0·052
M. triceps left	**0·79**	**0·33**	**0·52**
	P<0·001	P=0·170	P=0·031
M. biceps left	**0·85**	**0·54**	**0·61**
	P<0·001	P=0·018	P=0·009
M. triceps right	**0·75**	**0·48**	**0·39**
	P<0·001	P=0·039	P=0·123
M. biceps right	**0·79**	**0·51**	**0·50**
	P<0·001	P=0·027	P=0·039

Maximum workload is significantly correlated with muscle forces, with BMI and with Borg fatigue. Borg fatigue is correlated with almost all muscle forces. BMI is also significantly correlated with almost all muscle forces (Table 6).

Multiple regression analyses were performed with MFI-20 dimensions as dependent variables and FEV_1, all muscle forces, maximum workload and BMI as the independent variables. The regression equation for general and mental fatigue revealed no statistically significant contribution of the independent variables selected. For reduced activity and reduced motivation, only FEV_1 (% predicted) explained variance, 39% and 30% respectively:

- reduced activity= − 0·11 FEV_1 (% predicted)+18·99
- reduced motivation= − 0·14 FEV_1 (% predicted+ 16·99
- Concerning physical fatigue, 37% of the variance was explained by the muscle force of the left triceps:
- physical fatigue= − 0·002 M (triceps left)+24·76

Discussion

Data from this study show that subscale dimensions of subjective fatigue in patients with COPD are related to physiological variables, specifically pulmonary function and peripheral skeletal muscle force.

Our data suggest that patients with COPD suffer more from fatigue than healthy subjects. Given the prevalence and sometimes serious consequences of fatigue it is important to have a valid and reliable instrument to assess subjective fatigue as an independent variable. Furthermore subjective fatigue is a multidimensional concept. A one-dimensional approach includes the possibility of an incomplete description of the fatigue experiences of patients. Therefore we used the MFI-20 to determine fatigue in COPD patients. It is a short multidimensional questionnaire that does not contain any somatic items. This to exclude the risk of contamination of fatigue with somatic illness (16). The main difference with respect to a quality-of-life questionnaire is that fatigue used in the MFI-20 is an independent multidimensional entity.

In the present study, we determined the relationship between specific dimensions of subjective fatigue and physical variables. Peripheral muscle force is negatively correlated with physical fatigue, in COPD, such that patients with relatively low muscle force experience greater perception of subjective physical fatigue. It is possible that changes in physiological function contribute to the sensation of physical fatigue. Muscle force in patients with COPD may be reduced secondary to depletion and alteration in muscle metabolism. Furthermore, muscle force can be considered as one of the factors reflecting the general physical condition of the patient. Muscle force may be reduced in patients with pulmonary disease. These hypotheses are based on a relatively small number of patients in our study. Despite this small number significant correlations were found and the results are in agreement with earlier studies. Gosselink *et al.* (12) showed that hand grip force and quadriceps force decreased in patients with COPD as compared with healthy subjects. In addition, respiratory failure has been previously associated with correlates of reduced muscle force, smaller cross-sectional area of leg muscles (23) and muscle fibre atrophy (24). Reduction in muscle force in COPD may be related to alterations in muscle metabolism and extremity muscle fatigue, which, in turn, may be associated with the perception of physical fatigue. Patients with COPD have a decreased oxidative capacity of their skeletal muscles as compared with healthy subjects (25). Although these changes are probably not associated with maximal isometric muscle force, it is likely that they affect physiological fatigue of skeletal muscles and the endurance capacity. Similarly to the aforementioned relationship between the sensation of subjective physical fatigue and changes in muscle force in patients with COPD, alterations in physiological muscle fatigue may contribute to the sensation of physical fatigue in patients with COPD.

Another potential contributing factor to reduced muscle force is malnutrition. Malnutrition is reported to be common in patients with COPD (26). Reduced muscle force, in this context, can be considered one of the factors reflecting the general physical condition, including the nutritional state of the patient. In our study we showed that muscle force was positively correlated with nutritional status as estimated by the BMI, such that the higher the nutritional state of the subject, the greater was the force development capacity. Thus, muscle force is negatively influenced by altered nutritional status in patients with COPD. This was previously demonstrated by Fiaccadori *et al.* who indicated that malnutrition is related to a decrease in muscle force (27). A lower muscle force implies that a greater relative force, as a percentage of the maximum force in COPD, is needed for daily activities and exercise. This reduction in muscle force may be associated with the earlier onset of physiological fatigue or the perception of physical fatigue during activities in patients with COPD.

A trend for correlation between subjective physical fatigue and exercise capacity is shown in this study. In addition, reduced motivation shows strong correlations with dyspnoea and with subjective fatigue during the symptom-limited exercise test. It is possible that motivation to carry out daily life activities is reduced because of symptoms that may arise with activity. On the other hand, it is possible that patients with poor motivation to perform routine activities experience symptoms that are more pronounced during activities.

The result of this study that muscle force is positively correlated with exercise capacity is consistent with the work of Gosselink *et al.* (12) who showed that peripheral muscle weakness is associated with exercise limitation. We observed too a relationship between nutritional status and these outcomes. Altered nutritional status may lead to reduction in muscle force as well as exercise capacity. The data from this study show that subjective muscle fatigue measured by the Borg scale is correlated with exercise capacity in COPD. This correlation between subjective muscle fatigue and leg exercise capacity might indicate a cause–effect relation. However, muscle fatigue is also related to muscle forces of the upper arm muscles. A cause-and-effect relationship is in this case unlikely. As previously indicated, altered nutritional status may cause atrophy and weakness of all skeletal muscles. Impaired peripheral muscle force may contribute to subjective muscle fatigue, which, in turn, may lead to a symptom-limited reduction in exercise tolerance.

Reduced activity and reduced motivation show a significant correlation with FEV_1. These results indicate that airway obstruction is associated with reductions in both activity performance and the motivation to carry out activities. This relationship between fatigue and physical fatigue may contribute to the debilitative cycle in patients with COPD: impaired pulmonary function, reduced activity and fatigue. This, in turn, may have a negative impact on the motivation to carry out daily activities.

Conclusion

Fatigue may be an important symptom in patients with COPD. When there are signs that a patient is suffering from fatigue, the assessment should, in addition to pulmonary function, also be focused on peripheral muscle force. Muscle force training may be effective in these circumstance but further studies are needed to investigate this hypothesis.

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