Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease

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The relationship between tissue depletion and decreased exercise performance has been well established in patients with COPD. In this study we investigated the influence of the pattern of tissue depletion on health related quality of life (HRQL) and their mutual relationship with exercise capacity and dyspnoea.

Patients with low body weight and/or low fat-free mass (FFM; using bioelectrical impedance) were categorized in three groups according to type of tissue depletion: loss of both FFM and fat mass (FM), and loss of FFM or FM only. Handgrip strength (HGS) was used as a functional outcome measure of tissue depletion. Exercise performance was assessed by 12 min walking distance (12MWD) and dyspnoea by visual analogue scale (VAS). HRQL was measured with the St George's Respiratory Questionnaire (SGRQ) and the Medical Psychological Questionnaire for Lung diseases (MPQL).

Patients with depletion of FFM irrespective of body weight showed greater impairment in 12MWD, HGS, the ‘activity’ and ‘impact’ scores of the SGRQ and the domain ‘invalidity’ of the MPQL, in comparison with depleted patients with relative preservation of FFM. Exercise performance and dyspnoea were also significantly related to these subscores of HRQL. In addition, dyspnoea related significantly to the domain ‘symptoms’ of the SGRQ. Tissue depletion pattern remained significantly related to SGRQ-scores and the domain ‘invalidity’ of the MPQL when dyspnoea and walking distance were added to the model as a covariates.

Tissue depletion is an important determinant of HRQL independent of exercise capacity and dyspnoea.

Key words: COPD; quality of life; body composition; pulmonary rehabilitation.

Introduction

Pulmonary rehabilitation is presently defined by the ERS task force on rehabilitation and chronic care as a process which systematically uses scientifically based diagnostic, management and evaluation options to achieve the optimal daily functioning and health related quality of life of individual patients suffering from impairment and disability due to chronic respiratory disease, as measured by clinically and/or physiologically relevant outcome measures (1).

The basic assumption of this definition is that in pulmonary rehabilitation a number of treatments are used in a logical and systemic fashion based on the recognition that the impairment due to the chronic respiratory disease leads to disability and reduction in quality of life. The conceptual framework for understanding the dimensions of the consequences of the disease, and the relationship between them is set down in the International Classification of Impairments, Disabilities and Handicaps (ICIDH) published by the World Health Organization (WHO) (2). Accordingly, impairment, is defined as ‘any loss or abnormality of psychological, physiological or anatomical structure or function’; disability, is defined as ‘any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being’; handicap, refers to ‘a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfillment of a role that is normal (depending on age, sex, social and cultural factors) for that individual’ (2).

In using the concept of this framework, we hypothesized that in chronic obstructive pulmonary disease (COPD) the disease specific impairment may be two-fold: impairment of the respiratory organ system itself, including the ventilatory pump, reflected by abnormal measures of lung and pump function, and systemic impairment, which is manifested as muscle wasting and changes in muscle metabolism, and is reflected by alternations in muscle function. Dyspnoea and decreased exercise performance can then be considered to
be the disabilitating consequences of both the local and systemic impairment, whereas handicap may represent the disease specific health related quality of life (Fig. 1).

Several studies have demonstrated that pulmonary rehabilitation clearly improves health related quality of life in COPD patients. In a meta-analysis combining 14 trials available in medical literature, Lacasse et al. (3) found improvements in maximal exercise capacity and functional exercise capacity, associated to improvements in health related quality of life.

To be able to select the best possible candidates for rehabilitation and to provide an individually based programme, more insight is needed into the determinants of quality of life. It is clearly established that resting lung function measures are poorly related to quality of life (4–7). This is perhaps not surprising since lung function is moderately related to exercise capacity (8–11). Several studies by our group and others have clearly shown in recent years that tissue depletion is related to impaired exercise capacity (12,13). Only limited information is available regarding the relationship between weight loss and changes in body composition with quality of life. Weight loss commonly occurs in patients with severe COPD (14). Furthermore several studies have shown that depletion of fat-free mass may also occur in COPD despite a normal stable body weight (12,15). In particular, loss of fat-free mass has been shown to contribute to exercise impairment in COPD (12–14).

Based on the clearly established relationship between tissue depletion and decreased exercise tolerance in COPD we hypothesized a relationship between tissue depletion and health related quality of life. The aim of the present study was therefore specifically to study the influence of the pattern of tissue depletion on health related quality of life in a group of COPD patients at risk. We furthermore tried to gain more insight in the mutual relationship between measures of tissue depletion, functional impairment and HRQL.

**Methods**

**PATIENTS**

The study group consisted of patients with COPD, according to American Thoracic Society (ATS) guidelines (16), admitted to the pulmonary rehabilitation centre. All patients were in a stable clinical condition and none suffered from concomitant, confounding disorders. They were studied in the evaluation phase prior to entering the rehabilitation programme. Patients were consecutively included into the study if they suffered from a low body weight [body mass index (BMI); weight(kg)/height(m)²] and/or a low fat-free mass index [FFMI; fat-free mass (kg)/height(m)²].

**BODY COMPOSITION**

Body height was measured standing barefoot and determined to the nearest 0.5 cm. Body weight was measured with a beam scale to the nearest 0.1 kg without shoes and wearing light clothing. Fat-free mass (FFM) was measured by the bioelectrical impedance method. The resistance (BIA 101; RJL Systems, Detroit, MI, U.S.A.) was measured in the supine position at the right side. FFM was calculated from height²/resistance and body weight using a group specific regression equation derived from a previous study using deuterium dilution as a reference method (17).

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**Fig. 1.** Conceptual framework of International Classification of Impairments, Disabilities and Handicaps (ICIDH) applied to COPD.
LUNG FUNCTION TESTS
Lung function measurements included forced expiratory volume in 1 sec (FEV₁) and the forced vital capacity (FVC) (Masterlab; Jaeger Wurzburg, Germany). The best of three efforts was selected. All volumes were expressed as a percentage of the reference values (18).

MUSCLE FUNCTION
Muscle function was assessed by respiratory muscle strength and handgrip strength. Inspiratory respiratory muscle strength were determined by measuring respiratory mouth pressures using the method of Black and Hyatt (19). Maximal inspiratory mouth pressure (Pmax) was measured at residual volume (RV). The highest value of three manoeuvres was selected. Pmax measurement results in a negative pressure, but in the present study it was expressed and analysed in positive values. Values are expressed in absolute terms.

Handgrip strength was used as a simple measure of peripheral muscle strength. The force of the hand muscles was measured with a Jamar Hand Dynamometer (Preston, Jackson, Michigan, U.S.A.) on the non-dominant side with the subject sitting, the forearm and hand in a direct line with each other and resting on an armchair. At least three isometric contractions at 1 min intervals were performed. The best of three readings was used for further analysis. Values are expressed as kilogram force (kgf).

EXERCISE PERFORMANCE
Exercise performance was measured by a 12-min walking test (12MWD), performed in a level enclosed corridor. Patients were asked to walk as far as possible in 12 min. They could determine their own pace, even stop if necessary, and they were instructed that at the end they should feel as though they could not have walked any further. No encouragement during the test was given. The test was performed at a standardized item (between 13.00 and 14.00 h), and all patients performed one practice 12 min walking test.

DYSPNOEA
Patients were asked to rate their level of dyspnoea before performing the 12-min walking test using a visual analogue scale (VAS) of 100 mm length (20). Dyspnoea was expressed in mm, ranging from 0 to 100 mm.

HEALTH RELATED QUALITY OF LIFE
Health related quality of life (HRQL) was measured with the St. George's Respiratory Questionnaire (SGRQ) (21) and the Medical Psychological Questionnaire for Lung Diseases (MPQL) (22). The SGRQ, a 76 item respiratory-specific measure of HRQL has a total score, plus subscores for symptoms, activity and impact. The ‘symptoms’ component contains items on the level of symptomatology including frequency of cough, sputum production, wheeze and breathlessness. The ‘activity’ component is concerned with physical activities that either cause or are limited by breathlessness. The ‘impact’ component covers such factors as employment, being in control of health, panic, medication need and side effects, and the disturbance of daily life. The three components of HRQL are scored separately in the range from 0 to 100 with a score of zero indicating no impairment.

Since the SGRQ does not include a psychological dimension, the components ‘well-being’ and ‘experienced invalidity’ from the MPQL were added. ‘Well-being’ consists of 13 items [scores range from 13 (very unfavourable) to 39 (very favourable)] and measures mainly the state of mind including anxiety. ‘Experienced invalidity’ consists of 11 items [scores range from 11 (very favourable) to 33 (very unfavourable)] measuring a person’s perceived limitations in physical activities due to his illness. Patients were asked whether they agreed (score of 1), did not know (score of 2), or disagreed (score of 3) with the described items.

RESULTS
Table 1 summarizes the characteristics of the study group consisting of 32 men and 13 women with severe COPD (total group: FEV₁ 33±12%pred.; FVC 81±18%pred.) All patients participated in an inpatient pulmonary rehabilitation programme. Categorization by pattern of tissue depletion showed that 26 patients (58%) suffered from a loss of FM and FFM, seven patients (16%) had only a low FM and 12 patients (26%) showed a loss of FFM in spite of normal body weight.

Males and females were equally distributed between groups, while patients in group 2 were younger.
No differences were found between groups in FEV$_1$ and FVC.

There was a significant relationship between category of tissue depletion pattern and 12MWD (Fig. 2); in both groups of patients with depletion of FFM irrespective of body weight the distance walked was significantly lower (group 1: 640 ± 219 m, group 3: 585 ± 193 m), compared to the patients with a low FM only (836 ± 156 m).

Peripheral muscle strength, i.e. handgrip strength, was also significantly related to the category of body composition showing a similar pattern as was found for 12MWD (Fig. 3).

Respiratory muscle strength as determined by respiratory mouth pressures was lower in both patient groups with loss of FFM compared to patients with a low FM only, but this difference reached only statistically significance in group 1 compared to group 2 patients ($P < 0.05$). VAS scores, reflecting the sensation of dyspnoea at rest, were low in all patient groups and were not different between the groups.

The relationship between category of tissue depletion pattern and SGRQ subscores is given in Fig. 4. Patients with a low FFM irrespective of low body weight had significantly higher (i.e. greater impairment) ‘activity’ subscores compared to the patients with a low FM only (group 1: $65 ± 23$ vs. group 2: $45 ± 22$, $P < 0.05$ and group 3: $78 ± 14$, vs. group 2, $P < 0.05$). No difference in ‘activity’ score was found between groups 1 and 3.

The ‘impact’ subscore of the SGRQ was significantly higher (i.e. greater impairment) in the subgroup of patients with a low FFM only (group 3: $53 ± 15$ vs. group 1: $39 ± 16$, $P < 0.05$ and group 3 vs. group 2: $25 ± 21$, $P < 0.05$).

No differences between groups were found for the subscore ‘symptoms’ of the SGRQ. Figure 4 depicts the results of the MPQL. The component ‘well being’ was not different between the patient groups (group 1: $24 ± 8$; group 2: $26.0 ± 5.0$; group 3: $19.0 ± 8$). Significantly higher values for the component ‘invalidity’ indicative for more severe impairment were found in both patient groups suffering from loss of FFM (group 1: $30 ± 3$ vs. group 2: $26 ± 4$ $P < 0.05$; group 3: $32 ± 2$ vs. group 2, $P < 0.05$).

The correlation coefficients between measures of functional impairment and disability with HRQL were as
follows. Measurements of lung function (FEV\textsubscript{1} and FVC), ventilatory pump function (P\textsubscript{i}-max) and peripheral muscle strength (HGS) were not significantly correlated with subscores of the SGRQ or MPQL.

12MWD was significantly related to the SGRQ ‘activity’ score (r = -0.51; P < 0.01) and ‘impact’ score (r = -0.47; P < 0.01) as well as to the component ‘invalidity’ of the MPQL (r = -0.44; P < 0.05).

Dyspnoea related significantly to the SGRQ dimensions ‘impact’ and ‘symptoms’; correlation coefficients for this variable and SGRQ subscores were r = 0.44 (P < 0.05) respectively. However, dyspnoea was not significantly related to the domains of the MPQL.

Results of analysis of covariance between the pattern of tissue depletion and HRQL after adjustment for measures of functional impairment were as follows (Table 2): when handgrip strength and 12MWD were added to the model as covariates, the pattern of tissue depletion was not significantly related to the SGRQ. However, tissue depletion pattern remained independently related to the component ‘invalidity’ of the MPQL.

When P\textsubscript{i}-max was added as a covariate instead of handgrip strength the tissue depletion pattern remained independently related to the domains ‘activity’ and ‘impact’ of the SGRQ and to the component ‘invalidity’ of the MPQL.

A similar pattern was seen when analysis of covariance was done based on the pattern of tissue depletion, controlling for the covariates P\textsubscript{i}-max and dyspnoea. Dyspnoea related significantly to all subscores of the SGRQ, except for an independent relationship with the ‘symptoms’ domain of the SGRQ. Again, here the tissue depletion pattern remained independently related to the domains ‘activity’ and ‘impact’ of the SGRQ and to the component ‘invalidity’ of the MPQL.

Discussion

In this study we were particularly interested in the influence of the pattern of tissue depletion on health related quality of life, next to the influence of functional impairment in these patients. We therefore focused on patients considered to be depleted on the basis of decreased BMI and/or FFMI.

We found that patients exhibiting a depletion of fat free mass, irrespective of body weight, had significantly higher values of the ‘activity’ component of the SGRQ, indicative for reduced quality of life. Particularly the patients in group 3 displaying a low FFM only, were characterized by higher values for the subscore ‘impact’. The higher ‘impact’ score of patients in group 3 probably reflects a worse functional status in this group of patients compared to patients in group 2, since ‘impact’ connotes the ability to perform (and enjoy) the activities of daily life, including self-care skills and mobility. This could be reflected in the higher ‘activity’ score, indicative for more severe impairment, and the more reduced exercise performance in these patients compared to patients in group 2.

No significant difference was found between the groups for the subscore ‘symptoms’ of the SGRQ comprising items related to the level of symptomatology. Nevertheless, our results are in keeping with the results of the study by Shoup et al. (23) who observed that abnormally low fat-free mass in patients with COPD was related to greater impairment in all three subscores of the SGRQ.

In an earlier study by Ketelaars et al. (5) we found that the HRQL components ‘activity’ and ‘impact’ were negatively correlated with the results of the 12 min walking test. Although these relationships were significant, the correlations coefficient values (r) were low, r = -0.39 and r = -0.36 respectively. Furthermore, the 12 min walking test could only partly explain the variance in the subscores ‘activity’ (R\textsuperscript{2} = 0.15) and ‘impact’ (R\textsuperscript{2} = 0.25) of the SGRQ.
These findings are consistent with the outcome of a review of the literature recently given by Curtis et al. (24) who also observed weak but significant correlations (r-values ranging from 0.07 – 0.41) between different variables of HRQL and exercise tolerance, with an estimate of the proportion of the variability in HRQL of $R^2 = 0.27$.

In this study we found that body composition categories were also related to the ‘activity’ and ‘impact’ SGRQ scores, but walking distance was slightly better in predicting HRQL. The relevance of changes in body composition has been shown in its adverse effect on physical performance (12,13) as in 12 min walking. In addition it was recently demonstrated that in patients with COPD the 12 min walking test is performed at a relatively high metabolic and ventilatory stress close to the stress developed at an incremental symptom limited test on a cycle ergometer (25). This can be attributed to the loss of FFM which has been associated with atrophy of fast-twitch fibres in striated muscle.
higher deadspace/VT ratio, as was demonstrated in COPD patients. Finally, a less efficient breathing pattern, that is, fatiguability, and hence impaired exercise tolerance in these muscles (13) have been postulated to explain early onset of anaerobic glycolysis (25, 26) and metabolic acidosis (13, 27) and a decrease of local energy stores of exercising muscles in these patients, reflecting both loss of FFM as well as the underlying metabolic changes. This suggests that the effects of abnormalities in nutritional status on HRQL could be mediated through changes in exercise ability. This finding is in contrast with the results of Shoup et al. (23), who found that lean body mass categories were not significantly related to walking distance. However, we used the 12MWD which has been shown to be more discriminative (12) than the 6 min walking distance used in their study. In addition to the relationship between the pattern of tissue depletion and the domains of the SGRQ we found that tissue depletion pattern was significantly correlated with the subscore ‘experienced invalidity’ of the MPQL. Furthermore, this subscore was significantly correlated with exercise performance as measured by the 12 min walking distance. This is in accordance with the results of other investigators, who also found a significantly relationship between ‘experienced invalidity’ and exercise performance as measured by the maximal load reached on a bicycle ergometer \( r = -0.28 \), \( P < 0.001 \) and the 12 min walking test \( r = -0.28 \), \( P < 0.01 \) (22). Moreover, we found that tissue depletion pattern remained significantly related to the component ‘experienced invalidity’ of the MPQL when walking distance was entered as a covariate to the model. This suggests that the pattern of tissue depletion contributes also directly to HRQL as measured by the MPQL, independent of exercise tolerance.

In this study we used handgrip strength as a measure of peripheral muscle function. Muscle strength was significantly lower in patients with loss of fat-free mass. Muscle function is directly related to muscle mass and muscle morphology. The reduction in peripheral muscle strength can be explained by loss of fat-free mass since muscle mass has been found to correlate strongly with muscle strength in healthy older subjects (28). Furthermore, in depleted patients with COPD changes in fibre composition of the striated muscle has been found, that is a decrease in type II fibres with relative sparing of the type I fibres, resulting in an impaired maximum power output of the muscles.

Weakness of peripheral muscles with lower values of quadriceps muscle force compared to hand grip force has been observed in patients with COPD (29). Although we used HGS as a measure of peripheral muscle strength and found it to be reduced in depleted patients, it seems reasonable to expect that also quadriceps muscle force was reduced in our patients (29). Reduced quadriceps force has been shown not only to correlate with exercise limitation in patients with COPD, but also with the use of healthcare resources and limited self-care capabilities of these patients (30), suggestive of worse HRQL. It can therefore be speculated that the effect of impaired peripheral muscle function, i.e. HGS on HRQL, could be mediated through its effect on exercise performance.

In all patients low values for \( P_{1\text{-max}} \) were found indicative of compromised ventilatory pump function. However, no significant difference between body composition categories was observed. The mechanisms leading to a diminished function of the peripheral muscles—as was observed in this study—are not likely to spare the respiratory muscles. Indeed, several studies have reported on the relationship between respiratory muscle dysfunction and muscle wasting, both in COPD patients (31–34) as well as in non-COPD patients (35). However, the decrease in

### Table 2. Results of analyses of covariance between tissue depletion pattern and HRQL adjusted for handgrip strength, walking distance, \( P_{1\text{-max}} \) and dyspnoea

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<th>Covariates</th>
<th>SGRQ</th>
<th>MPQL</th>
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<td></td>
<td>activity</td>
<td>impact</td>
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<tr>
<td>Pattern of depletion</td>
<td>n.s.</td>
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<tr>
<td>handgrip strength</td>
<td>n.s.</td>
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<tr>
<td>walking distance</td>
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<td>( P_{1\text{-max}} )</td>
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<td>( P_{1\text{-max}} )</td>
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<td>dyspnoea</td>
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n.s.: not significant.
ventilatory pump function that has been observed in patients with COPD also stems from the mechanical disadvantage to the (accessory) inspiratory muscles, including the diaphragm, to hyperinflation (36, 37). Both factors together are responsible for the observed decrease in respiratory muscle function in these patients. For this reason, a decrease in FFM would not necessarily lead to detectable differences in respiratory muscle strength, and hence P\textsubscript{r}-max.

In this study dyspnoea was the only factor related to all subscores of the SGRQ in addition to its relationship with ‘experienced invalidity’ of the MPQL. This is in accordance with the studies by Mahler et al. who demonstrated that dyspnoea as measured by the baseline dyspnoea index (BDI) was the single most important factor related to general health status as measured by the Short Form-36 questionnaire and the severity of dyspnoea was a significant predictor of the various components of HRQL (38). Also, Shoup et al. (23) recently found that dyspnoea, measured by BDI, was the strongest factor related to health related quality of life as measured by the SGRQ. However, we found that tissue depletion pattern was independently related to the subscales ‘activity’ and ‘impact’ of the SGRQ when dyspnoea was added as a covariate to the model. This is in contrast with the results of the study by Shoup et al. (23) who were unable to find such a relationship. This is probably caused by the inclusion of overweight patients in their study group, while we studied a more homogeneous group of patients that were only included if they suffered from tissue depletion.

In summary, this study shows that tissue depletion is a determining factor of health related quality of life as measured by the SGRQ independent of exercise performance and the sensation of breathlessness.

In correspondence with the ICIDH-concept, impairment in COPD should be considered to be of a local and a systemic nature, each with a separate and identifiable influence on disability and handicap, i.e. quality of life. The distinctions between impairment, disability and handicap are both meaningful and important in pulmonary rehabilitation in order to focus on the individual requirements and available treatment options for patients with chronic respiratory disease. Whether reversion of depletion will improve quality of life remains to be studied.

References

18. Quanjer PH, Tammeling GJ, Cotes JE. Symbols, abbreviations and units. Working party standardization


