Extra-pulmonary features in COPD patients entering rehabilitation after stratification for MRC dyspnea grade

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KEYWORDS
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Summary
Experts have stated that referral for rehabilitation of patients with chronic obstructive pulmonary disease (COPD) becomes appropriate when these patients become aware of their disability (e.g. usually grade 3 to 5 on the Medical Research Council (MRC) dyspnea scale). However, patients with MRC dyspnea grade 1/2 may also suffer from extra-pulmonary features, such as abnormal body composition, exercise intolerance and reduced disease-specific health status. In the present study, we have studied whether and to what extent chronic obstructive pulmonary disease (COPD) patients with MRC dyspnea grade 1/2 have extra-pulmonary features compared to patients with grade 3, 4 or 5?
Pulmonary function, body composition, 6-min walking distance, peak exercise capacity, anxiety, depression and disease-specific health status have been assessed in 333 outpatients who had been referred for pulmonary rehabilitation. On average, patients with MRC dyspnea grade 1/2 had a better exercise tolerance and disease-specific health status compared to patients with grade 4 or 5. Nevertheless, grade 1/2 patients had a higher prevalence of muscle mass depletion. In addition, these patients did still have aberrant values in one or more of the aforementioned outcomes.
Introduction

Patients with moderate to severe chronic obstructive pulmonary disease (COPD) may suffer every day from dyspnea. The degree of severity of dyspnea perception and its repercussions on daily functioning have been assessed regularly in patients with moderate to severe COPD and have been shown to be worse compared to healthy age-matched control subjects. The Medical Research Council (MRC) scale is a simple measure of dyspnea, which has shown to be more discriminating than staging of disease severity of the American Thoracic Society with respect to 5-year survival of patients with COPD. Furthermore, the MRC dyspnea scale has been suggested in recent international guidelines to identify COPD patients that may benefit from rehabilitation (e.g. usually grades 3 to 5). This suggestion has been based on experts opinion that rehabilitation of patients with COPD becomes appropriate when these patients become aware of their disability, irrespective of their pulmonary dysfunction. In fact, COPD patients entering rehabilitation with MRC dyspnea grade 3 or above have been shown to have a clear exercise intolerance, reduced disease-specific health status, reduced mood status and reduced self-reported daily physical activity, especially in COPD patients with grade 5. Unfortunately, Bestall and colleagues did not enroll COPD patients with MRC dyspnea grade 1/2, given that these grades correspond to mild disability due to dyspnea. In spite of this, it is still reasonable to hypothesize that COPD patients with lower MRC dyspnea grades (grade 1 or 2) can still suffer from extra-pulmonary features (i.e. exercise capacity, body composition and disease-specific health status), which may partly improve following pulmonary rehabilitation.

For instance, a mean 6-min walking distance (6MWD) of only 71% predicted has been found in COPD patients entering rehabilitation with MRC dyspnea grade 1/2. Moreover, mean body mass index (BMI, body weight (kg) divided by squared height (m)) tended to be significantly lower in COPD patients entering pulmonary rehabilitation with MRC dyspnea grade 1/2 than those of patients with MRC dyspnea grade 3/4. Even though this unexpected finding was not significant, it is reminiscent for the possible existence of disparities in body composition after stratification for MRC dyspnea grades. Finally, median scores on the domain symptoms of the St. George’s Respiratory Questionnaire (SGRQ) in male COPD outpatients with MRC dyspnea grade 2 were comparable to those of patients with dyspnea grade 3 or above. Actually, the mean total SGRQ scores of grade 1/2 COPD patients entering rehabilitation were clearly worse than values obtained in healthy elderly.

At present, it remains unknown whether and to what extent extra-pulmonary features are different after stratification for MRC dyspnea grades in a large cohort of consecutive COPD patients referred for rehabilitation by their chest physician.

Methods

Patients

Pulmonary function, dyspnea, body composition, exercise capacity, mood status and disease-specific health status have been assessed prospectively between January 1, 2005 to November 1, 2006 in 333 consecutive patients with moderate to severe COPD. Additionally, self-reported co-existing morbidity was assessed using the Charlson comorbidity index.

All patients were admitted to the Centre for Integrated Rehabilitation of Organ failure (CIRO) to undergo a 3-day intake/assessment program before the start of a comprehensive interdisciplinary pulmonary rehabilitation program.

Previously, the use of long-term oxygen therapy has been shown to be related to hospital admission rate in COPD, which, in turn has been shown to clearly affect disease-specific health status. Therefore, patients who were on long-term oxygen therapy were not included in the present analyses. All tests were performed in the clinical routine and were in accordance with World Medical Association declaration of Helsinki. All participants were Caucasian and gave informed consent. The local Medical Ethical Commission approved this observational study.

Assessments

Pulmonary function and arterial blood gases

Forced expiratory volume in the 1 s (FEV1) and forced vital capacity (FVC) were calculated from the flow–volume curve using spirometry. FEV1 was also calculated 15 min after inhalation of a β agonist via a metered dose inhaler. Carbon monoxide transfer factor of the lung (DLCO) was determined using the single breath method. Lung function parameters were expressed as a percentage of reference values. Arterial oxygen tension (PaO2), arterial carbon dioxide tension (PaCO2) and arterial oxygen saturation (SaO2) were analyzed with a blood gas analyzer.
Dyspnea
Self-perceived dyspnea in relation to physical disability has been assessed by using the MRC dyspnea scale. COPD patients had to grade their self-perceived dyspnea by using pre-defined statements, e.g. (1) "I only get breathless with strenuous exercise"; (2) "I get short of breath when hurrying on the level or up a slight hill"; (3) "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"; (4) "I stop for breath after walking 100 yards or after a few minutes on the level"; and (5) "I am too breathless to leave the house or breathless when dressing or undressing".

Body composition
Body composition was assessed by using single-frequency bioelectrical impedance assessment after overnight fasting. Fat-free mass was calculated by using validated COPD-specific equations. A priori, a BMI <21 kg/m² and a fat-free mass index (FFMI, fat-free mass in kilogram divided by squared height in meters, f/m) <15/16 kg/m² have been defined as abnormally low.

Exercise capacity
Peak cycling load and peak aerobic capacity (VO₂) have been assessed by using a symptom-limited incremental ergometry cycling test and were normalized for age, sex and height. In addition, functional exercise capacity has been assessed by using a 6MWD test and were expressed in percentage (%) predicted.

Mood status
Anxiety and depression have been assessed using the Hospital Anxiety and Depression Scale (HADS). A priori, a score of ≥10 points for anxiety and/or depression had been defined as abnormally high and may be suggestive for the presence of clinically relevant symptoms of anxiety and/or depression. Scores can range from 0 (optimal) to 21 points (worst).

Disease-specific health status
SGRQ has been used to assess disease-specific health status. It consists of three domains (symptoms, activity and impact) and a total score. Scores can range from 0 (optimal) to 100 points (worst).

Statistics
All statistics were done using GraphPad Prism 4.03 and SPSS 14.0. Obtained values have been tested for normality and are presented as mean (standard deviation, SD). Patients were stratified by self-reported MRC dyspnea grades. Due to the low number of COPD patients with MRC dyspnea grade 1 (n = 9), the authors have decided a posteriori to combine patients with MRC dyspnea grade 1/2 or grade 3, but was significantly lower compared to values obtained in patients with MRC dyspnea grade 1/2 or grade 3. Differences in DLCO disappeared after correction for alveolar surface.

Results
General characteristics
Patients generally had mild to severe COPD (FEV₁: 45.9±15.0% predicted; FEV₁/FVC: 44.1±12.9%), normal arterial blood gases (PaO₂: 9.3±1.2 kPa; PaCO₂: 5.3±0.7 kPa), normal body composition (BMI: 25.1±5.0 kg/m²; FFMI (f/m): 15.4±2.0/17.1±2.1 kg/m²), functional exercise intolerance (6MWD: 69.7±16.3% predicted), peak exercise intolerance (VO₂: 64.5±24.5% predicted; peak cycling load: 56.7±22.5% predicted), normal mood status (anxiety: 6.9±4.7 points; depression: 6.9±4.1 points) and reduced disease-specific health status (total SGRQ score: 55.0±17.0 points). In addition, patients had a mean MRC dyspnea grade of 3.6±1.2.

Stratification by MRC dyspnea grades
Characteristics
Mean age and scores on the Charlson comorbidity index were not significantly different between MRC dyspnea grades (Table 1). Patients with MRC dyspnea grade 1/2 had a significantly better FEV₁ than patients with grade 3, 4 or 5. In addition, patients with MRC dyspnea grade 1/2 or grade 3 (Table 2). In contrast, the degree of severity of airway obstruction was comparable between MRC strata (Table 1). Static lung hyperinflation was comparable between patients with MRC dyspnea grade 1/2 or grade 3, but was significantly lower compared to patients with grade 4 or 5. DLCO was comparable between patients with MRC dyspnea grade 1/2 or grade 3, but was significantly better compared to patients with grade 4 or 5. Differences in DLCO disappeared after correction for alveolar surface.

Body composition
Patients with MRC dyspnea grade 1/2 had a high mean BMI, which was significantly higher than values obtained in patients with MRC dyspnea grade 1/2 or grade 3 (Table 2). Additionally, 27.6% of the patients with MRC dyspnea grade 1/2 had an abnormal low BMI, which tended to be less prevalent in patients with MRC dyspnea grade 4 (14.8%, p = 0.086).

On average, FFMI was comparable between the MRC strata in female and male patients (Table 2). Then again, the prevalence of an abnormal low FFMI was significantly higher in the grade 1/2 patients (48.3%) than in grade 4 patients (27.9%, p = 0.022).

Functional exercise capacity
Functional exercise capacity was clearly reduced in all MRC strata (Table 2). Nevertheless, patients with MRC dyspnea grade 1/2 had a significantly better absolute 6MWD than patients with grade 3, 4 or 5. In addition, grade 3 patients...
had a better 6MWD than patients with MRC dyspnea grade 4 or 5.

After correction for gender, age, height and body weight, significant differences were found between patients with grade 1/2 and grade 4 or 5; between patients with grade 3 and grade 4 or 5; and between patients with grade 4 and grade 5 (Figure 1).

Changes in transcutaneous oxygen saturation following the 6MWD test were comparable between the MRC strata, as well as peak heart rate and symptom Borg score for fatigue at the end of 6MWD test (Table 2). In contrast, symptom Borg score for dyspnea at the end of 6MWD test was significantly lower in patients with grade 1/2 compared to patients with grade 4 or 5. In addition, patients with MRC dyspnea grade 3 perceived less breathlessness at the end of the 6WMD test than patients with grade 5.

Peak exercise capacity

Absolute peak cycling load was significantly different between the MRC strata, except for the difference between patients with grades 4 and 5. These differences remained significant after correction for gender, age and height (Table 2).

Patients with MRC dyspnea grade 1/2 had a significantly better peak VO\textsubscript{2} per kilogram body weight than patients with grade 3, 4 or 5. Additionally, patients with MRC dyspnea grade 3 had a significantly better peak VO\textsubscript{2} per kilogram body weight than patients with grade 4 or 5. Conversely, after expressing peak oxygen uptake as a percentage of the reference values of Jones and colleagues, there were only significant differences between patients with MRC dyspnea grade 1/2 and 5; and grades 3 and 5.

Peak heart rate was significantly higher in patients with MRC dyspnea grade 1/2 compared to grade 3, 4 or 5. In addition, patients with MRC dyspnea grade 3 had significantly higher mean peak heart rate compared to patients with grade 4 or 5.

Patients with MRC dyspnea grade 3 had significantly higher absolute minute ventilation than patients with grade 4 or 5. In addition, patients with MRC dyspnea grade 1/2 had significantly higher absolute minute ventilation than patients with grade 4 or 5. In contrast, patients with MRC dyspnea grade 4 or 5 had relatively higher minute ventilation than grade 1/2 patients. Symptom Borg scores for dyspnea and fatigue and changes in transcutaneous \textit{S}\text{aO}\textsubscript{2} were not significantly different between MRC strata (Table 2).

Mood status

Significant differences in HADS anxiety score were found between patients with MRC dyspnea grades 3 and 5, and between grades 4 and 5 (Table 3). Patients with MRC dyspnea grades 1/2 or 3 had lower (= better) HADS depression scores than grade 5 patients. Additionally, 40.7% and 43.5% of the grade 5 patients had an abnormal high score for anxiety and depression, respectively. The prevalence of increased HADS scores for anxiety and depression was lower in patients with grade 1/2 (27.8%, \(p = 0.006\) and 20.8%, \(p = 0.118\), respectively) or grade 3 (19.6%, \(p = 0.001\) and 23.1%, \(p = 0.001\), respectively).

Disease-specific health status

Significant differences in the three SGRQ domains between the different MRC strata have resulted in significant
differences in SGRQ total scores between all MRC strata (Table 3). Thus, patients with a lower MRC dyspnea grade had significantly lower (\(=\) better) SGRQ total scores than patients with higher MRC dyspnea grades (Figure 2).

Discussion

The present study demonstrates significant differences in extra-pulmonary features in a large cohort of patients with COPD entering pulmonary rehabilitation after stratification for MRC dyspnea grades.

Body composition

Previously, mean BMI tended to be significantly lower in COPD patients entering rehabilitation with MRC dyspnea grade 1/2 (26.3 kg/m\(^2\)) than those with MRC dyspnea grade 3/4 (29.2 kg/m\(^2\)). In the present study, grade 4 patients also had a high mean BMI, which was significantly higher than the normal mean BMI of patients with MRC dyspnea grade 1/2 or 3 (Table 2). Indeed, a higher mean BMI may explain to some extent a higher dyspnea perception in daily life. Then again, underweight COPD patients (mean BMI: 18.7 kg/m\(^2\)) have been shown to have a significantly worse mean modified MRC dyspnea grade than normal weight peers (mean BMI: 24.5 kg/m\(^2\)).

Table 2  Outcomes of physical fitness.

<table>
<thead>
<tr>
<th></th>
<th>Grades 1/2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>ANOVA</th>
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<tbody>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
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</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>24.1 (4.5)</td>
<td>24.6 (4.1)</td>
<td>26.3 (6.1)</td>
<td>25.5 (5.2)</td>
<td>0.0441</td>
</tr>
<tr>
<td>FFMI (f), kg/m(^2)</td>
<td>14.8 (1.4)</td>
<td>15.2 (1.7)</td>
<td>16.0 (2.7)</td>
<td>15.5 (2.0)</td>
<td>0.1557</td>
</tr>
<tr>
<td>FFM (m), kg/m(^2)</td>
<td>16.8 (2.0)</td>
<td>17.0 (1.8)</td>
<td>17.7 (2.6)</td>
<td>17.1 (2.2)</td>
<td>0.3104</td>
</tr>
<tr>
<td><strong>6MWD</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Meters</td>
<td>525.0 (92.5)</td>
<td>492.7 (87.9)</td>
<td>412.4 (95.8)</td>
<td>383.2 (104.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% predicted</td>
<td>80.2 (14.2)</td>
<td>75.9 (13.4)</td>
<td>65.7 (13.6)</td>
<td>59.8 (15.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ΔSaO(_2) %</td>
<td>-3.4 (4.2)</td>
<td>-4.8 (4.6)</td>
<td>-4.7 (4.6)</td>
<td>-3.7 (4.2)</td>
<td>0.1027</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>107.9 (17.6)</td>
<td>109.9 (16.4)</td>
<td>104.7 (16.4)</td>
<td>105.1 (17.7)</td>
<td>0.1254</td>
</tr>
<tr>
<td>Dyspnea end</td>
<td>3.4 (1.8)</td>
<td>4.1 (2.1)</td>
<td>4.7 (2.3)</td>
<td>4.9 (2.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fatigue end</td>
<td>3.4 (2.2)</td>
<td>3.7 (2.3)</td>
<td>3.9 (2.5)</td>
<td>4.0 (2.4)</td>
<td>0.4800</td>
</tr>
</tbody>
</table>

Values expressed as mean (SD). Body mass index (BMI), kilogram (kg), squared meter (m\(^2\)), fat-free mass index (FFMI), female (f), male (m), oxygen uptake (VO\(_2\)), transcutaneous oxygen saturation (tSaO\(_2\)), heart rate (HR), beats per minute (bpm), ventilation (VE), maximal voluntary ventilation (MVV), liters (l), minute.

Post-hoc: *p < 0.01 versus grade 1/2; \#p < 0.05 versus grade 1/2; †p < 0.01 versus grade 3; \*p < 0.05 versus grade 3; \‡p < 0.01 versus grade 4.

Figure 1  Functional exercise intolerance.
The present authors were not able to corroborate these findings. Even though the mean FFMI was similar amongst the MRC strata after stratification for gender, 48.3% of the COPD patients with MRC dyspnea grade 1/2 had an abnormal low FFMI, which may partly be related to daily physical inactivity in patients with COPD.29 This suggests the possible existence of a reduced daily physical activity level in a subgroup of COPD patients with MRC dyspnea grade 1/2. Indeed, patients may modify their daily behavior (e.g. less weight-bearing activities and/or a lower effort patients may exert in completing activities of daily life) to avoid unpleasant sensations of dyspnea.30 In fact, an a posteriori analysis has been shown that grade 1/2 patients with a normal FFMI tended to have a higher FEV1 than grade 1/2 patients with an abnormal FFMI (58.3 versus 52.3% predicted, p = 0.08). Then again, daily physical activity level has been shown to be reduced in patients with COPD compared to healthy age-matched subjects, irrespective of the degree of pulmonary function impairment.29 Therefore, other underlying factors may to some degree have contributed to FFM depletion in a subgroup of COPD patients with MRC dyspnea grade 1/2.31–33

Exercise intolerance

In the present study, patients with MRC dyspnea grades 1/2 had the best 6MWD compared to patients with a higher MRC dyspnea grade (Table 2, Figure 1). These findings are in line with previous findings.9,34 These data suggest that functional exercise capacity is related to the degree of severity of dyspnea perceived during daily life. In fact, patients with MRC dyspnea grade 4 or 5 had also the worst symptom Borg scores for dyspnea at the end of the 6MWD. Furthermore, the mean difference in 6MWD between patients with MRC dyspnea grade 1/2 and grade 4 (112.7 m) or grade 5 (141.9 m) clearly exceeded the minimum clinically important difference of 54 m.35 COPD patients with MRC dyspnea grade 5 had the worst peak exercise capacity of all MRC strata, as seen previously.9 Nevertheless, a decreased mean peak exercise capacity has been found in all MRC strata (Table 2). Indeed, mean peak oxygen uptake of all MRC strata was clearly below the lower limit of normal as proposed in the latest statement on cardiopulmonary exercise testing by the American Thoracic Society and the American College of Chest Physicians (lower limit of normal for peak VO2: 85% predicted).36

A clear difference has been observed between MRC strata concerning peak heart rate and peak minute ventilation at the end of the symptom-limited incremental exercise test (Table 2). In fact, patients with MRC dyspnea grade 1/2 generally have been shown to have a cardio-circulatory limitation, which makes them most probably good candidates for an endurance-type of exercise training.6,19,37 In contrast, patients with grade 4 or 5 were generally ventilatory limited, which makes them most probably good

### Table 3  Mood and health status.

<table>
<thead>
<tr>
<th></th>
<th>Grades 1/2</th>
<th>Grade 5</th>
<th>ANOVA</th>
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<tbody>
<tr>
<td><strong>HADS (n = 299)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety, points</td>
<td>6.9 (4.9)</td>
<td>6.0 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Depression, points</td>
<td>6.3 (4.0)</td>
<td>6.2 (3.8)</td>
<td></td>
</tr>
<tr>
<td><strong>SGRQ (n = 290)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms, points</td>
<td>54.6 (20.9)</td>
<td>61.7 (18.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Activity, points</td>
<td>50.5 (18.1)</td>
<td>64.8 (17.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impact, points</td>
<td>31.0 (17.9)</td>
<td>40.5 (18.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total score, points</td>
<td>40.8 (16.6)</td>
<td>51.3 (15.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values expressed as mean (SD). Hospital Anxiety and Depression Scale (HADS), St. George’s Respiratory Questionnaire (SGRQ). Post-hoc: *p ≤ 0.01 versus grade 1/2; †p ≤ 0.05 versus grade 3; ‡p ≤ 0.05 versus grade 1/2; ††p ≤ 0.05 versus grade 3; †††p ≤ 0.01 versus grade 4; ††††p ≤ 0.05 versus grade 4.
candidates for an interval-type of training to improve exercise tolerance. The latter patients may even improve their exercise tolerance by performing progressive resistance training or transcutaneous neuromuscular electrical stimulation.

**Mood status**

Recently, the mean scores on the Brief Assessment Schedule Depression Cards were not different between COPD patients entering rehabilitation with MRC dyspnea grade 1/2, 3/4 or 5. On the contrary, higher HADS scores for anxiety and depression have been reported in COPD patients entering pulmonary rehabilitation with MRC dyspnea grade 5 compared to lower grades. The latter finding has been corroborated in the present study (Table 3). It seems therefore reasonable to hypothesize that the presence of anxiety and/or depression is, at least in part, related to the perceived dyspnea during daily life in COPD. In fact, patients with severe COPD had a 2.5 times greater risk for depression than healthy control subjects. Moreover, dyspnea has shown to be significantly related to depression in elderly patients with recent hospitalization for acutely decompensated heart failure.

**Disease-specific health status**

Previously, male COPD outpatients with MRC dyspnea grade 2 have shown to have lower median total SGRQ scores compared to patients with severe dyspnea (e.g. combination of grades 3, 4 and 5). The present study is the first to observe significant differences in SGRQ total scores between all MRC strata in a large group of consecutive patients with COPD (Table 3, Figure 2). In fact, mean differences in total SGRQ scores between patients with MRC dyspnea grade 1/2 and patients with grade 3, 4 or 5 were approximately a three fold, four fold and six fold of the minimum clinically important difference of 4 points, respectively. It is therefore reasonable to conclude that dyspnea is a strong determinant of disease-specific health status. However, patients who do not experience extreme dyspnea during activities of daily life (e.g. MRC dyspnea grade 1/2) appear to still have an increased (= worse) mean total SGRQ score compared to values obtained in healthy elderly. This is in line with Garrod and colleagues. These findings point strongly toward the fact that COPD patients with MRC dyspnea grade 1/2 may still have a reduced disease-specific health status. Therefore, other factors besides dyspnea may, at least in part, also contribute to a decreased disease-specific health status in patients with COPD.

**Pulmonary rehabilitation**

In the recent past, the MRC dyspnea scale has been suggested and used to select COPD patients who may benefit from rehabilitation. This suggestion has been based on experts opinion that rehabilitation of patients with COPD becomes appropriate when these patients become aware of their disability, irrespective of their pulmonary dysfunction. Actually, COPD patients with MRC grade 1 or 2 have been excluded from a rehabilitation program as being ‘too fit’. However, the present results clearly indicate that COPD patients referred for rehabilitation with MRC grade 1/2 may have extra-pulmonary features, which most probably can be addressed during a comprehensive interdisciplinary pulmonary rehabilitation program. Indeed, Garrod and colleagues have shown significant mean improvements in 6MWD (+55 m) and total SGRQ score (~7.5 points) in COPD patients with baseline MRC dyspnea grade 1/2 following 7 weeks of twice-weekly outpatient exercise training and patient education. The latter improvements were comparable to those of COPD patients with baseline MRC dyspnea grade 3/4 and were significantly better than those of COPD patients with baseline MRC dyspnea grade 5. In addition, COPD patients with somewhat ventilatory reserve during a baseline symptom-limited incremental cycling test have been shown to be the best responders during a 6-month exercise training program. In the present study, this would be the grade 1/2 patients (Table 2). Finally, elderly patients may also benefit from physical exercise training, while they most probably will have a MRC dyspnea grade 1 at baseline. Therefore, it appears reasonable to hypothesize that the MRC dyspnea scale alone is not an ideal measure to identify COPD patients who may benefit from rehabilitation. Based on the present results, it may be reasonable to add the bioelectrical impedance assessment. Indeed, the MRC dyspnea scale (e.g. grade 3 or above) together with the overnight fasting bioelectrical impedance assessment (e.g. an abnormal low FFMI) identified already 91% of the present patients entering pulmonary rehabilitation.

**Limitations of the present study**

Preferably, healthy controls should have been included in the present study to demonstrate the presence of extra-pulmonary features in COPD patients, in particular in those with MRC dyspnea grade 1/2. Nevertheless, to determine the presence of extra-pulmonary features in the present COPD patients have been based on internationally well-established cut-off values obtained in healthy age-matched control subjects. The presence of whole-body muscle mass depletion may have been an important reason to refer COPD patients with MRC dyspnea grade 1/2 for rehabilitation. This, in turn, may have resulted in a selection bias. However, the prevalence of cachexia in the present COPD patients with MRC dyspnea grade 1/2 is in agreement with findings in Dutch COPD outpatients with MRC dyspnea grade 1/2 who volunteered to participate in the COSMIC trial.

Statistically significant differences between self-reported MRC dyspnea grades need to be interpreted in the light of the number of comparisons that were made in the present study. Nonetheless, the current statistical procedures have been used to test pre-defined hypotheses. Finally, the present authors want to stress that they have been using the original MRC dyspnea scale as done before, while others have been using various modifications of the MRC scale. Although the different versions of the MRC dyspnea scales are rather
comparable to the original MRC dyspnea scale, their scoring is slightly different and may therefore be somewhat misleading.

Conclusions

At present, the MRC dyspnea scale does provide an indication of the degree of severity concerning extra-pulmonary features in patients with moderate to severe COPD entering rehabilitation. Nevertheless, the MRC dyspnea scale is inadequate to identify extra-pulmonary features in the clinical practice in individual patients with COPD. Therefore, MRC dyspnea scale alone does not appear to be a suitable measure to identify most patients with COPD who have to be referred for rehabilitation. Future studies are warranted to determine whether chest physicians can use the MRC dyspnea scale and the overnight fasting bioelectrical-impedance assessment together to identify COPD patients at the outpatient consultation for pulmonary rehabilitation.

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Conflict of interest statement

The authors do not have any conflict of interest with the contents of the present manuscript.

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