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Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): The Maugeri Study

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Summary

While the effectiveness of pulmonary rehabilitation (PR) in chronic obstructive pulmonary disease (COPD) is well established, its effectiveness in the most severe category of COPD, i.e. patients with chronic respiratory failure (CRF), is less well known.

Objective: To verify the effects of PR in patients with CRF, and compare the level of improvement with PR in these patients to that of COPDs not affected by CRF.

Methods: A multi-centre study was carried out on COPD patients with versus without CRF. The PR program included educational support, exercise training, and nutritional and psychological counselling. Lung function, arterial gases, walk test (6MWT), dyspnoea (MRC; BDI/TDI), and quality of life (MRF₂₈; SGRQ) were evaluated.

Results: Thousand forty seven consecutive COPD inpatients (327 with CRF) were evaluated. In patients with CRF all parameters improved after PR (0.001). Mean changes: FEV₁, 112 ml; PaO₂, 3.0 mmHg; PaCO₂, 3.3 mmHg; 6MWT, 48 m; MRC, 0.85 units; MRF₂₈ total score, 11.5 units. These changes were similar to those observed in patients without CRF.

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Conclusions: This study, featuring the largest cohort so far reported in the literature, shows that PR is equally effective in the more severe COPD patients, i.e. those with CRF, and supports the prescription of PR also in these patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) determines high morbidity and mortality. To date, it represents the fourth leading cause of death in Europe and the United States,^{1,2} and by 2020 it will rank third.³ Pulmonary rehabilitation (PR) is recognized as a cornerstone of COPD treatment: it ameliorates symptoms and exercise capacity, and constitutes one of the few ways of improving health status.⁴ The growing interest in PR is testified by the fact that major scientific societies have each published specific guidelines on the subject.^{5–7} More recently, a joint statement of the American Thoracic Society and the European Respiratory Society on PR described patient assessment, exercise training, education, nutritional support, and psychosocial support as integral parts of PR.⁸ Expected benefits from PR are reduced dyspnoea level, improved exercise tolerance, and maximized patients' health-related quality of life (HRQoL).⁵

Almost all the studies demonstrating the efficacy of PR have included COPD patients at various stages of the disease, including subgroups of patients with severe COPD. However, in these studies COPD patients with chronic respiratory failure (CRF) were either excluded or they were lumped together with other COPD patients without CRF. Similarly, meta-analyses on PR^{9–11} either excluded studies involving patients with CRF or included patients with severe COPD without giving information on the presence or not of CRF. Thus, none of the papers included in these meta-analyses has focused explicitly on the efficacy of PR in CRF.

On the other hand, over recent years it has become increasingly evident that many patients enrolled in PR programmes have severe COPD, mostly with CRF.

To verify whether a PR programme can improve the outcome also in COPD patients with CRF, and to compare the level of improvement in these patients to that of COPD patients without CRF, we conducted a large multi-centre observational study, the Maugeri Study. To the best of our knowledge this is the first study designed to test the hypothesis that PR is effective also in severe COPD with CRF.

Methods

The "Salvatore Maugeri" Foundation Ethical Committee approved the study (143CEC/2001). Patients gave their informed consent to participate in the study.

The non-profit "Salvatore Maugeri" Foundation is the largest Italian institution (2052 beds) devoted to rehabilitation. It numbers several institutes throughout Italy. In its respiratory units common protocols for PR are applied, and usually all activities are planned and coordinated by an inter-institute Central Department. In seven of these units (Campoli/Telese, Cassano Murge, Lumezzane/Gussago, Montescano, Pavia, Tradate, Veruno), over a period of 24 months

(April 2001–April 2003), we collected data from 1130 consecutive inpatients with stable COPD (with or without CRF) who underwent an inpatient PR program.

All patients were diagnosed with COPD according to GOLD criteria.²

All patients were suffering from dyspnoea, reduced exercise tolerance, muscle deconditioning or limitation of daily-life activities, but were in stable clinical conditions. Medical therapy had to be optimized before recruitment of subjects. Patients suffering from acute exacerbation (i.e. requiring antibiotics, oral/parenteral steroids or an increase of oxygen or bronchodilators over the previous 4 weeks) and patients with lack of motivation or poor compliance, neuromuscular disorders, unstable angina, or recent (i.e. <6 months) myocardial infarction were excluded from the PR program. Patients were hospitalized and all the costs were supported by the Italian National Health System.

CRF was defined as a condition in which patients had an arterial oxygen tension (PaO_2) <60 mmHg requiring long-term oxygen therapy and/or arterial carbon dioxide tension ($PaCO_2$) >45 mmHg.^{12,13}

Patients underwent a comprehensive PR programme consisting of: (a) verbal inputs stressing the need for adherence to therapy, (b) educational support, (c) exercise training, and (d) a nutritional intervention and psychological counselling, if needed. The rehabilitation program was completely tailored to suit the needs of the individual.

According to guideline recommendations,^{5–7} the exercise programme was also tailored to the individual and a group of exercises was chosen for each patient^{5–7} according to their ability to tolerate exercise and their disease severity (e.g. some patients were prescribed cycling training, others walking training; some patients needed also postural exercises, etc.). The programme consisted, on average, of five supervised daily sessions per week of: (a) aerobic exercise training (cycling, walking, or arm exercise), (b) respiratory muscle training, (c) breathing exercise, (d) postural exercises, and (e) upper- and lower-body muscle strength training exercises. Exercises were graded, i.e. their intensity weekly increased as the patient progressed in the programme.¹⁴ Patients with CRF were provided with ambulatory oxygen during the exercise sessions. The exercise programme was supervised by a chest physiotherapist.

The outcome measures were dyspnoea, exercise capacity and HRQoL,⁶ which were measured in all patients together with spirometry and blood gas analysis. All measurements were assessed at admission and at the end of the PR programme. Dyspnoea was assessed by the Medical Research Council (MRC) dyspnoea scale¹⁵ and the baseline/transitional dyspnoea index (BDI/TDI).¹⁶ Exercise capacity was evaluated by means of the 6 min walking test (6MWT).¹⁷

Health status—HRQoL was evaluated through the following questionnaires¹⁸: all patients with CRF received the Maugeri Respiratory Failure Questionnaire (MRF₂₈)¹⁹; patients without CRF were administered the St. George's

Respiratory Questionnaire (SGRQ).^{20,21} To perform a comparison between groups and verify the questionnaires' discriminative capacity and sensitivity to changes, a randomly selected subgroup of 77 patients with CRF was administered also the SGRQ, and a subgroup of 93 patients without CRF was administered also the MRF₂₈.

The MRF₂₈ is the only questionnaire specifically designed for CRF. It has been translated into: Czech, English (Canada, UK, USA), French (Canada, Switzerland), German, Italian, Japanese, Portuguese (Brazil), and Spanish. Its 28 items are grouped around three specific factors: *daily activity*, associated with disability in daily life due to breathlessness; *cognitive function*, related to impaired cognitive function; *invalidity*, related to the experience of social isolation or dependency on others. The MRF₂₈ total and subscale scores range from 0% (best health status) to 100% (poorest health status).¹⁹

Spirometry and arterial blood gas analysis were performed according to guidelines.^{22,23} Arterial blood was sampled whilst patients were breathing room air.

Statistical analysis

Descriptive statistics were performed for all the recorded variables. Baseline characteristics between the two groups (CRF versus non-CRF) were compared by means of unpaired *t*-test. The efficacy of PR was assessed by comparing the difference in the evaluated parameters between baseline and post-treatment data. A repeated measures analysis of covariance (baseline level used as covariate) model was applied to test both pre-post-treatment differences within the two groups and trends over time between groups. Results are shown as change between post-treatment and baseline levels (Δ values). For SGRQ and MRF₂₈ questionnaires, analyses were performed on the total as well as subscale scores. Threshold for statistical significance was set at 0.05.

Results

Baseline characteristics

A total of 1130 consecutive COPD patients were recruited; 83 subjects dropped out during the rehabilitation programme. Therefore, the sample for analysis consisted of 1047 patients, of whom 327 patients (31.2%) were affected by CRF. Patients' mean baseline characteristics are shown in Table 1.

Patients were in the 70-year age group and, on average, overweight (body mass index (BMI) higher than 24.9). In particular, the percentage of overweight patients was 63% in the CRF group and 58.9% in the non-CRF group ($p = \text{NS}$). Patients in the CRF group were more impaired in terms of airway obstruction ($p = 0.001$), walked fewer meters during the 6MWT ($p = 0.001$) and were more dyspnoeic ($p = 0.001$) than patients in the non-CRF group.

In the CRF group the most compromised MRF₂₈ scores were Activity and Invalidity. Impairment in Cognitive function, although present, was less important. In the non-CRF group, the SGRQ Activity and Symptoms scores were more impaired than the Impact score. Interestingly, in the subgroups in which both questionnaires were assessed

Table 1 Baseline characteristics (mean value \pm SD) of the two groups of COPD patients.

Parameter	CRF	Non-CRF	<i>p</i> -Value
Number	327	720	
Males/females	251/76	604/116	0.008
Age (years)	69.6 \pm 7.9	68.9 \pm 8.8	NS
BMI (kg/m ²)	27.2 \pm 5.7	26.6 \pm 5.5	NS
FVC (% predicted)	61.7 \pm 16.4	74.5 \pm 16.3	0.001
FEV ₁ (% predicted)	37.3 \pm 14.3	48.6 \pm 15.9	0.001
RV (% predicted)	154.1 \pm 61.9	155.4 \pm 53.8	NS
pH (units)	7.42 \pm 0.04 [‡]	7.43 \pm 0.03	0.01
PaO ₂ (mmHg)	53.7 \pm 6.1 [‡]	71.2 \pm 7.9	0.001
PaCO ₂ (mmHg)	46.9 \pm 8.7 [‡]	38.8 \pm 4.7	0.001
6MWT (m)	283.3 \pm 106.2	360.2 \pm 110.5	0.001
MRC*	3.75 \pm 1.16	3.21 \pm 1.17	0.001
BDI [†]	4.09 \pm 2.06	5.2 \pm 2.36	0.001
MRF ₂₈ —Total score	53.7 \pm 23.5	46.4 \pm 23.7 [§]	0.01 [§]
MRF ₂₈ —Activity	64.1 \pm 27.5	56.8 \pm 27.3 [§]	0.04 [§]
MRF ₂₈ —Cognitive function	58.9 \pm 26.9	57.4 \pm 27.7 [§]	NS [§]
MRF ₂₈ —Invalidity	66.9 \pm 28.0	63.5 \pm 27.4 [§]	0.02 [§]
SGRQ—Total score	38.8 \pm 16.1	41.1 \pm 16.9	NS
SGRQ—Symptoms	53.0 \pm 19.2	49.6 \pm 21.7	NS
SGRQ—Activity	52.6 \pm 22.5	52.7 \pm 20.7	NS
SGRQ—Impact	27.2 \pm 15.0	32.7 \pm 18.2	0.004

COPD, chronic obstructive pulmonary disease; CRF, chronic respiratory failure; BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in the 1 s; RV, residual volume; pH, hydrogen-ion concentration; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; 6MWT, 6-min walking test; MRC, Medical Research Council dyspnoea scale; BDI, baseline dyspnoea index; MRF₂₈, Mageri Foundation Respiratory Failure questionnaire; SGRQ, St. George's Respiratory Questionnaire.

*Higher score indicates worse dyspnoea level.

[†]Lower score indicates worse dyspnoea level.

[‡]Arterial blood was sampled whilst patients were breathing room air.

[§]MRF₂₈ was also tested in a subgroup ($n = 93$) of COPD patients without CRF for comparison (*in italics*).

^{||}The SGRQ was also tested in a subgroup ($n = 77$) of COPD patients with CRF for comparison (*in italics*).

the SGRQ did not show any difference between the two groups apart from the Impact score, whereas the MRF₂₈ showed more impaired scores in the CRF group, with the exception of the Cognitive function score.

Apart from the prescription of long-term oxygen therapy (LTOT), there was no substantial difference in the chronic baseline prescription of pharmacologic therapy between the two groups of patients.

Effects of PR in the whole sample

The average duration of the PR programme was 24 \pm 4 (SD) days. At the end of PR, an improvement in dyspnoea (TDI and MRC), exercise capacity (MRF₂₈ and SGRQ), and pulmonary function was found in all patients. In particular, MRC improved (mean \pm SE) by 19.6 \pm 0.8%, walking distance by 19.6 \pm 1.4%, MRF₂₈ total score by 23.5 \pm 2.5%, SGRQ total

score by $19.6 \pm 3.1\%$, and forced expiratory volume in 1 s (FEV₁) by $14 \pm 0.9\%$. For all parameters the difference versus baseline was statistically significant ($p = 0.001$).

Comparing the effects of PR in CRF and non-CRF patients

Analysing data according to diagnostic groups, we found that both groups showed very similar patterns (Table 2). FEV₁ slightly improved; in the CRF group this improvement was on average 112 ml compared to 154 ml in the non-CRF group ($p = 0.03$ between groups, $p = 0.001$ versus baseline). The improvement in PaO₂ showed no difference between the two groups: 3.0 mmHg ($p = 0.01$) in the CRF group and 2.2 mmHg ($p = 0.05$) in the non-CRF group. PaCO₂ decreased by 3.3 mmHg in the CRF group ($p = 0.001$) and by 0.4 mmHg in the non-CRF group ($p = \text{NS}$) ($p = 0.001$ between groups). The distance walked during the 6MWT also showed a similar improvement in the two groups, of 48.2 m in the CRF and 47.8 m in the non-CRF group (both $p = 0.001$ versus baseline).

Dyspnoea was reduced in both groups after the PR programme ($p = \text{NS}$ between groups). The MRC score decreased by 0.85 and 0.73 units (both $p = 0.001$), and TDI was on average 3.68 and 3.78 in the CRF and non-CRF groups, respectively.

Also health status improved after rehabilitation. In the CRF group, all MRF₂₈ scores improved, from a minimum of 5.2 units (Cognitive function) to a maximum of 17.6 units (Activity). These improvements were highly significant

(Invalidity, Activity, and Total score, $p = 0.01$; Cognitive function, $p = 0.02$) (Figure 1).

In patients without CRF the SGRQ total score and all subscales (Symptoms, Activity, and Impact) showed a similar behaviour to that of the MRF₂₈ (Figure 2). All scores statistically improved ($p = 0.001$). For the Total and Impact scores improvement was also clinically significant, being >10 units for the Total score and >8 units for the Impact score, well over the 4 unit threshold for clinical significance.²⁴

As previously mentioned, the SGRQ was also administered to a subgroup of 77 CRF patients, and the MRF₂₈ to a subgroup of 93 patients without CRF. No differences in SGRQ were found between the two groups as the score decreased by 11.2 ± 0.6 units in the non-CRF group and by 8.1 ± 1.5 units in the CRF group ($p = \text{NS}$ between groups). Conversely, the improvement found in the MRF₂₈ was significantly higher in the CRF than in the non-CRF group (11.7 ± 1.3 versus 5.1 ± 1.3 ; $p = 0.001$ between groups).

Discussion

The present study evaluated the effectiveness of a comprehensive individually tailored PR programme in COPD patients with CRF, comparing its effects in this group with those in COPD patients not affected by CRF. Although it has been reported that PaO₂ and PaCO₂ are factors unrelated to the response to exercise training in COPD patients,²⁵ there has been little research on PR specifically targeted at CRF patients and to the best of our knowledge this is the first

Table 2 Variation of the principal parameters after rehabilitation (mean value \pm S.E.).

Parameter	CRF	Non-CRF	Between groups, <i>p</i> -value
Δ FEV ₁ (ml)	$112 \pm 1.5^\dagger$	$154 \pm 1.3^\dagger$	0.03
Δ PaO ₂ (mmHg)	$3.0 \pm 0.31^\dagger$	$2.2 \pm 0.35^\dagger$	NS
Δ PaCO ₂ (mmHg)*	$-3.3 \pm 0.45^\dagger$	$-0.4 \pm 0.20^\ddagger$	0.001
Δ 6MWT (m)	$48.2 \pm 4.3^\dagger$	$47.8 \pm 2.7^\dagger$	NS
Δ MRC*	$-0.85 \pm 0.06^\S$	$-0.73 \pm 0.03^\dagger$	NS
TDI	3.68 ± 0.15	3.78 ± 0.10	NS
Δ MRF ₂₈ —Total score* [¶]	$-10.5 \pm 1.2^{**}$	$-5.1 \pm 1.3^{**}$	0.002
Δ MRF ₂₈ —Activity* [¶]	$-15.4 \pm 1.7^{**}$	$-4.6 \pm 1.8^{**}$	0.001
Δ MRF ₂₈ —Cognitive* [¶]	$-3.2 \pm 2.0^{**}$	$-4.8 \pm 3.2^{**}$	NS
Δ MRF ₂₈ —Invalidity* [¶]	$-7.0 \pm 1.6^{**}$	$-7.9 \pm 2.3^{**}$	NS
Δ SGRQ—Total score* [¶]	$-8.3 \pm 1.5^{**}$	$-11.1 \pm 0.6^{**}$	NS
Δ SGRQ—Symptoms* [¶]	$-19.4 \pm 2.8^{**}$	$-16.6 \pm 0.8^{**}$	NS
Δ SGRQ—Activity* [¶]	$-5.9 \pm 2.1^{**}$	$-12.0 \pm 0.8^{**}$	0.007
Δ SGRQ—Impact* [¶]	$-5.9 \pm 1.4^{**}$	$-8.4 \pm 0.7^{**}$	NS

COPD, chronic obstructive pulmonary disease; CRF, chronic respiratory failure; BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in the 1 s; RV, residual volume; pH, hydrogen-ion concentration; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; 6MWT, 6-min walking test; MRC, Medical Research Council dyspnoea scale; BDI, baseline dyspnoea index; MRF₂₈, Mageri Foundation Respiratory Failure questionnaire; SGRQ, St. George's Respiratory Questionnaire.

*Reduction in score indicates improvement. For all other parameters, increase in score indicates improvement.

[†] $p = 0.001$ versus baseline.

[‡] $p = \text{NS}$ versus baseline.

[§] $p = 0.01$ versus baseline.

[¶]The SGRQ was also tested in a subgroup ($n = 77$) of COPD patients with CRF for comparison (*in italics*).

[¶]The MRF₂₈ was also tested in a subgroup ($n = 93$) of COPD patients without CRF for comparison (*in italics*).

**All differences between pre- and post-treatment data are significant, $p < 0.001$ except Δ MRF₂₈—Cognitive ($p = 0.04$). Significant interactions according to the ANOVA model have been shown for MRF₂₈—Total score ($p = 0.014$), MRF₂₈—Activity ($p = 0.001$) and SGRQ—Activity ($p = 0.013$), pointing out a more marked decrease in the CRF (MRF₂₈) and non-CRF (SGRQ) groups, respectively.

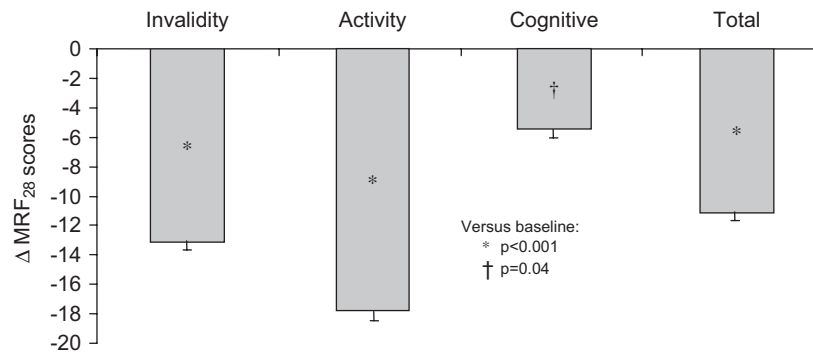


Figure 1 Improvement in MRF₂₈ scores (patients with CRF) (mean value \pm SE) after PR programme.

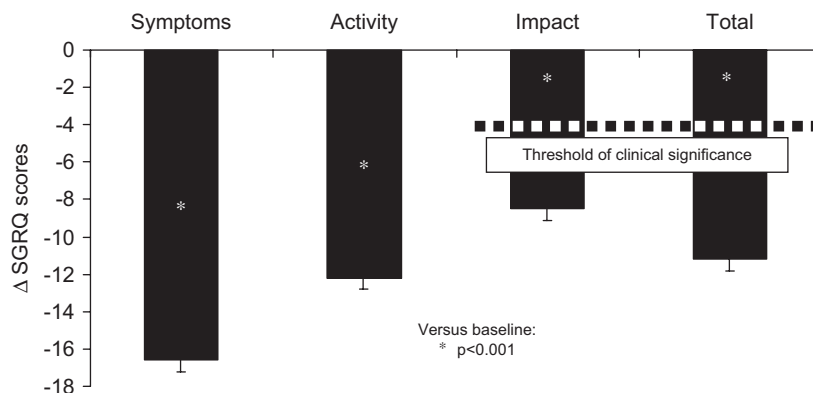


Figure 2 Improvement in SGRQ scores (patients without CRF) (mean value \pm SE) after PR programme.

study demonstrating, in a large cohort of >300 of COPD patients with CRF, that PR is effective also in this group.

Several meta-analyses have been published on PR.⁹⁻¹¹ One of these excluded from the analysis studies with patients requiring domiciliary oxygen.⁹ In the other two, generic subgroups of patients with severe COPD are described. However, none of the papers included in these two meta-analyses specifically evaluated patients with CRF. In some, in fact, patients were considered as very severe simply on the basis of a low FEV₁% predicted²⁶⁻²⁸ or a high score at the MRC scale²⁹; in other papers, the real need for O₂ therapy (i.e. blood gas analysis or oxygen prescription) was not described.³⁰

A few other studies evaluated the effects of PR in very severe COPD, i.e. patients at the extreme end of the disease spectrum such as COPD patients on LTOT.^{31,32} However, in these studies either the PaO₂ was not reported³¹ or the PR programme consisted of just one single session per week.³²

In our study all patients were hospitalized. Although in the United States inpatient rehabilitation is usually reserved for patients who are too disabled to travel to outpatient settings,³³ in Europe this is a quite common setting for PR,^{33,34} and in Italy the National Health System routinely reimburses all costs.

Lung function

Although it is generally thought that PR should not change the lung function of COPD patients, it has been reported

that an individualized, graded PR programme can determine an improvement in spirometry.^{31,35} Individualization and gradation of the PR programme such as we adopted in our protocol, rather than a uniform exercise protocol as is usually applied in heterogeneous patient populations, could therefore be a factor accounting for the improvement we found in lung function.

Another possible explanation is based on treatment compliance. Guidelines on PR state that stressing adherence to therapy through an educational intervention¹ should be a component part of the program. During the rehabilitation period, we stressed the need to adhere completely to the prescribed therapy as well as to the program. This might be one reason for the improvement we observed in both patient groups, with and without CRF. Notably, the greater improvement was observed in patients with CRF, indicating that airflow limitation may be ameliorated also in patients with more severe COPD.

Exercise tolerance

The distance walked similarly increased in the two groups of patients after PR, 17% in patients with CRF and 13% in COPD patients without CRF. In this regard, the increment might appear small, although not different between groups. However, it is worth noting that, especially in such compromised CRF subjects, also a little improvement may be subjectively valuable.

Moreover, a Cochrane Collaboration publication showed that the pooled effect size on 6MWT of the included randomized controlled trials is 49 m¹¹ and a recent “State-of-the-Art” review on PR⁴ showed that rehabilitation programmes including more sessions are more effective than programmes with fewer sessions (34.5 m with <28 sessions versus 50.3 m with >28 sessions). Consistent with this evidence, a mean improvement of about 48 m was found in both groups, who on average received 24 rehabilitative sessions. In addition, the percentage of patients who improved their walking ability by at least 54 m, i.e. the threshold considered significant for a clinically significant improvement after an intervention,³⁶ was 39.6% in the CRF group and 41.0% in the non-CRF group.

Symptoms

Dyspnoea was assessed by two different questionnaires. The MRC scale is simple to administer and not time consuming; however, it represents a unidimensional measure.¹⁶ Conversely, the BDI/TDI needs to be administered by an expert operator but has multidimensional properties.¹⁶ The improvement in dyspnoea level as measured by these two questionnaires was similar between the two groups of patients, although the CRF group showed a slightly better trend.

Quality of life

It is widely recognized that PR improves patients' HRQoL. We demonstrated that HRQoL improved also in the more severe COPD group, i.e. patients with CRF. Although measured by two different questionnaires, the pattern of improvement found was similar in the two groups. More interestingly, in the two subgroups that received both questionnaires, the pattern of response to the SGRQ and MRF₂₈ between the two groups was different. At baseline, the SGRQ was not able to differentiate between the two groups, apart from the Impact score, whereas the MRF₂₈ discriminated very well. After rehabilitation, we found no difference in score variation as measured by the SGRQ, apart from the Activity score. Conversely, the MRF₂₈ showed significant differences in improvement between the two groups of patients in both Total and Activity scores.

Similarly, Clini et al.³⁷ applied the SGRQ and MRF₂₈ to compare the efficacy of long-term non-invasive positive pressure ventilation (NPPV) plus LTOT versus LTOT alone in patients with COPD and CRF. In that study, the SGRQ did not show any difference between the two groups, but the MRF₂₈ appeared to be more specific and sensitive. At the end of the 2-year follow-up, patients on LTOT alone showed slightly worsened health status scores, measured with the MRF₂₈, whereas patients who received LTOT and NIPPV had improved scores.

Our findings together with Clini's confirm that for patients with respiratory failure a condition-specific questionnaire such as the MRF₂₈ may be more appropriate than a disease-specific questionnaire such as the SGRQ.

One possible limitation of the present study is that, in a study designed to evaluate the effects of PR in CRF, there was no control group of CRF patients who did not undergo

PR. However, our scope in this study was to verify if PR could have the same benefit in CRF as in non-CRF COPD patients; as a consequence, the COPD group without CRF constitutes the control group against which we compared the efficacy of PR in patients with CRF. A further point to consider is that it would have been non-ethical to deny PR to a subgroup of COPD patients—given the well-established efficacy of PR in COPD—particularly in an institution completely devoted to rehabilitation and with patients subsidized by the National Health System.

In conclusion, the present study demonstrates, in the largest cohort so far reported in the literature, that PR, known to be effective in COPD in general, is also equally effective in end-stage COPD, i.e. patients with CRF.

Conflict of interest

None of the authors have a conflict of interest to declare in relation to this work.

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