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Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: A comparison with patients with moderate-to-severe COPD

--Manuscript Draft--

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Abstract:	<p>Purpose: Pulmonary rehabilitation (PR) is effective in patients with moderate-to-severe COPD. However, the effects of PR in patients with mild COPD have not yet been established. Thus, this study investigated the short- and long-term effects of PR in patients with mild COPD in comparison with patients with moderate-to-severe disease.</p> <p>Methods: 32 patients with mild (Group 1) and 29 with moderate-to-severe (Group 2) COPD completed the study. Both groups participated in a 12-week PR program with exercise training and psychoeducation. Outcome measures at baseline, 3 (post-PR), 6 and 9 months included the 6-minute walk test (6MWT); the Modified Medical Research Council questionnaire; 1-repetition maximum on the chest press and knee extension; the Brief physical activity assessment; number of exacerbations on the past 3 months and the St George Respiratory Questionnaire (SGRQ).</p> <p>Results: Improvements in the 6MWT, chest press and knee extension and physical activity were observed post-PR ($p < 0.001$), with no differences between the two groups. Reduction in the number of exacerbations ($p < 0.001$) and improvements in the SGRQ total ($p < 0.001$) were also observed, however, with greater magnitude in group 2 ($p = 0.029$ and $p < 0.001$). Excepting peripheral muscle strength, all the achieved benefits were sustained at 6 and 9 months ($p > 0.05$).</p> <p>Conclusions: PR improves exercise tolerance, muscle strength, physical activity and health-related quality of life and reduces exacerbations in patients with mild COPD as in patients with moderate-to-severe COPD. Moreover, most of these benefits were maintained at 9 month follow-up, suggesting that PR could be part of the management of mild COPD.</p>
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Title: Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: A comparison with patients with moderate-to-severe COPD

Amendments following reviewer's recommendations

Dear Professor Larry F. Hamm,

We thank the editor and the reviewer for the time they spent considering our paper and for their valuable comments. We have made an attempt to address the specific recommendations, to allow them to make the final decision regarding the manuscript. Below we present the list of amendments that have been performed, following the list of comments.

Reviewer 1

In the Intervention section clarify what is meant by "The PR programs were conducted in the community." Were these hospital-based, walking programs in the park - much more detail is needed to clarify the setting of the study. Reference to community-based programs is made in the Discussion, page 9, so this clarification is of particular importance.

Thank you for your comment. The pulmonary rehabilitation program was implemented in a community primary care center. The content of the pulmonary rehabilitation program was consistent with international guidelines. In general, each session of exercise training comprised of five components: warm up, endurance training, strength training, balance training and cool down. A detailed description of each one of these components, as well as regarding the psychoeducation sessions, is provided elsewhere (Respir Care. 2014;59:1577-1582). This information has now been added to the Methods section as suggested. Please see page 2, lines 7-12.

"A 12-week PR program was delivered in a community primary-care center by three physical therapists. This program, described in detail elsewhere, was composed of 3 weekly sessions of exercise training (60 min) and 1 weekly session of psychoeducation (90 min).8 Each session of exercise training comprised of five components: warm up, endurance training, strength training, balance training and cool down. Patients with mild and with moderate-to-severe COPD trained together, which ensured a uniform training."

Also in the Intervention section clarify how the "same physical therapists" can work in 3 separate programs, this does not seem possible.

Three physical therapists implemented one pulmonary rehabilitation program in a community primary care center. This has now been clarified. Please see page 2, lines 7-8.

"A 12-week PR program was delivered in a community primary-care center by three physical therapists."

Clarify exactly what comparisons are being made between which cohorts of subjects. As there were drop-outs at each stage of testing, it needs to be made clear that the samples at each stage were still equivalent, and are comparisons at each stage being made between the final n or the subjects that are still in at each stage (which would be the correct comparison).

Thank you for your pertinent observation. Baseline characteristics between completers and dropouts were compared at each study time point (3, 6 and 9 months) and for each group separately. This has now been clarified both in the Methods (please see page 4, lines 3-7) and Results (please see page 4, lines 23-24) sections.

"Differences i) between completers and dropouts in each group at each time point, and ii) between patients with mild and moderate-to-severe COPD at baseline were tested"

"For each group, there were no significant differences between completers and dropouts at any time point ($p > 0.05$)."

The dropout rate was also analyzed per group and only then compared: "Dropouts were similar in both groups, with rates of 20 and 27.5% ($p = 0.300$)."(please see page 5, lines 3-4).

Similarly, it is stated that all programs used the same PTs to minimize training differences, however this should be demonstrated statistically with baseline and outcomes compared between the three programs.
Only one pulmonary rehabilitation program was designed and implemented. This has now been clarified. The 80 patients enrolled did not engage in the program at the same time, and that is the reason why the authors considered relevant to report that across all the study timeframe, the same three physical therapists were involved. We believe that this has now been clarified in the Methods section. Please see page 2, lines 7-8. "A 12-week PR program was delivered in a community primary-care center by three physical therapists."

The Discussion section is somewhat redundant with the results. Many of the paragraphs start with a re-stating of the results. These numbers are reported in the Results section and do not need to be restated in the Discussion. Please rewrite these paragraphs to be more concise.

Thank you for your valuable comment. The Discussion section has now been rewritten. Please see some examples below:

"The 6MWT improvement in patients with mild COPD was similar to that found in patients with moderate-to-severe COPD and it is in line with the range of values found in previous studies (34-60 meters)." (page 6, lines 27-29)

"Dyspnea improved significantly with PR, 19 yet this benefit was not observed in patients with moderate-to-severe COPD, contradicting earlier studies." (page 7, lines 8-9)

"In line with previous studies, 41, 42 PR resulted in improvements in peripheral muscle strength. But after the initial improvement, losses similar to those described in the literature were observed." (page 7, lines 17-19)

Title, change the "a" after the colon (:) to A - titles use the same grammatical rules as sentences.

Thank you for your suggestion. Title has now been edited accordingly.

Standardize the terms used to indicate the times periods for admission, discharge and follow-up testing. I would suggest baseline testing, PR discharge, 6 and 9 month follow-up.

Thank you for your valuable comment. To address your comment, the terms baseline (pre-PR), 3 (post-PR), 6 and 9 months follow-ups are used throughout the manuscript. We believe that these terms are those that better indicate the real timeline of the study. "Exercise tolerance, dyspnea, self-reported PA, history of exacerbations, HRQOL and peripheral muscle strength were assessed in a standardized order at baseline (pre-PR), and 3 (post-PR), 6 and 9 months later." (page 2, lines 20-22)

This also needs to be clarified in Figure 1 - no mention of Baseline testing (add this)
This has now been clarified and added. Please see figure 1.

Delineate paragraphs with an extra space at the start of each paragraph.

Thank you for your suggestion. This has been performed throughout the manuscript.

Introduction, First paragraph, line 21: change the word "latest" to "2013" - it may not be the latest guidelines when published or read.

Thank you for your pertinent observation. This word has been replaced (please see page 1, line 11).

"This has been identified by the 2013 American Thoracic Society/European Respiratory Society official statement on PR as a major research topic to be addressed"

Second paragraph, line 32: change "it is well known..." to "it has been shown..."
This expression has been replaced as suggested (please see page 1, lines 16-17).
"In patients with moderate-to-severe COPD, it has been shown that in the absence of any maintenance strategy,..."

Design and Participants, First paragraph, first sentence: add "non-experimental" before "prospective" to indicate this was not an RCT.
Thank you for your relevant suggestion. This has now been added (please see page 1, line 25).
"A non-experimental, prospective two-arm longitudinal study was conducted."

First paragraph, line 16: be specific as to which institutional ethic committees approved the study.
The institutional ethic committees that approved the study have now been added to the Methods section. Please see page 2, lines 1-3.
"The study was approved by the Center Health Regional Administration and from the National Data Protection Committee."

Results – Participants, Second paragraph, line 20: it is stated that none of the participants used long term oxygen therapy, however it would be interesting to know if any used oxygen to maintain exercise levels (a common occurrence in PR) and if this affected the results.
Thank you for your valuable comment. As participants were recruited from community primary care centers, even those with severe COPD had a relatively good health condition. This was expected since patients with more severe COPD, namely those with chronic respiratory failure, are generally followed in hospitals and not by their general practitioners. Thus, none of the included patients were using long-term oxygen therapy or presented major desaturation during exercise training. This information has now been added to the Results section (please see page 4, lines 26-27).
"None of the patients used long-term oxygen therapy or needed supplemental oxygen during exercise training."

Discussion, Page 8, line 53: change "around" to "of approximately".
This sentence has been rewritten (please see page 8, lines 1-2).
"The improvement in SGRQ exceeded the established minimal important difference and was sustained at 9 month follow-up."

Page 9, second sentence, line 3: delete this sentence "This finding...during the program". This is purely speculative and was not examined or measured in the present study.
Thank you for your pertinent comment. This sentence has now been deleted (page 8, line 5).

Page 9, last paragraph, line 57: Delete the word "Nevertheless" and start the sentence with "To..."
This has been modified accordingly (please see page 8, line 29).
"To assess the potential of PR to modify the disease trajectory in mild COPD, studies with longer follow-ups are recommended."

References, Need to be changed to meet APA guidelines.
References have now been formatted to meet JCPR guidelines.

Table 1: Not sure if Table 1 is necessary, this could be more concisely and clearly summarized in the Methods section
Thank you for your pertinent suggestion. Table 1 has now been removed and general information regarding the PR program is given in the Methods section. In addition, for more detailed information, readers can consult a pre-existing document which is now referenced. Please see page 2, lines 8-12.

"A 12-week PR program was delivered in a community primary-care center by three physical therapists. This program, described in detail elsewhere, was composed of 3 weekly sessions of exercise training (60 min) and 1 weekly session of psychoeducation (90 min).⁸ Each session of exercise training comprised of five components: warm up, endurance training, strength training, balance training and cool down."

Table 3: contains a mass of data, may be more understandable with separate tables for comparisons of each time period.

Thank you for your pertinent observation. To facilitate reading, Table 3 has now been splitted into two tables (please see table 2 and 3).

Figure 1: delete the box with "Enrollment" standing by itself; add in Baseline measurements; change wording of time periods to be standard with the paper throughout; are dropouts for "non-COPD reasons" the same as "health related reasons"? This should be made consistent and explained in the text of the paper. The box "Enrollment" has now been deleted and the information on "Baseline" added. Wording of time periods has now been standardized throughout the manuscript. Indeed, dropouts for "non-COPD reasons" are the same as "health related reasons". To avoid misunderstandings, "health-related reasons" have now been used throughout the manuscript.

Editorial Comment

The JCRP word count limitation for original manuscripts is 3,000 words. Your manuscript is currently at 3,133 words. Please decrease the total word count to conform with the Journal's requirement. This may be accomplished by editing as suggested in the Reviewer comment #6 above.

The word count of the revised manuscript is 2758, conforming with the requirements of the JCPR.

We look forward to your response.

Yours Sincerely,
Alda Marques

Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: A comparison with patients with moderate-to-severe COPD

Running head: Pulmonary rehabilitation in mild COPD

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Contributors

CJ performed data collection and analysis and drafted the manuscript. AM revised it critically for important intellectual content and provided final approval of the version to be published.

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Word count: 2758 words

Structured Abstract

Purpose: Pulmonary rehabilitation (PR) is effective in patients with moderate-to-severe COPD. However, the effects of PR in patients with mild COPD have not yet been established. Thus, this study **investigated** the short- and long-term effects of PR in patients with mild COPD in comparison with patients with moderate-to-severe disease.

Methods: 32 patients with mild (Group 1) and 29 with moderate-to-severe (Group 2) COPD completed the study. Both groups participated in a 12-week PR program with exercise training and psychoeducation. Outcome measures at baseline, **3 (post-PR), 6 and 9 months** included the 6-minute walk test (6MWT); the Modified Medical Research Council questionnaire; 1-repetition maximum on the chest press and knee extension; the Brief physical activity assessment; number of exacerbations on the past 3 months and the St George Respiratory Questionnaire (SGRQ).

Results: Improvements in the 6MWT, chest press and knee extension and physical activity were observed post-PR ($p<0.001$), with no differences between the two groups. Reduction in the number of exacerbations ($p<0.001$) and improvements in the SGRQ total ($p<0.001$) were also observed, however, with greater magnitude in group 2 ($p=0.029$ and $p<0.001$). Excepting peripheral muscle strength, all the achieved benefits were sustained **at 6 and 9 months** ($p>0.05$).

Conclusions: PR improves exercise tolerance, muscle strength, physical activity and health-related quality of life and reduces exacerbations in patients with mild COPD as in patients with moderate-to-severe COPD. Moreover, most of these benefits were **maintained at 9 month follow-up**, suggesting that PR could be part of the management of mild COPD.

Condensed Abstract

The disease-modifying potential of pulmonary rehabilitation in patients with mild COPD is not established. Results demonstrate that PR is effective in mild COPD as well as in moderate-to-severe COPD, suggesting that PR could be part of the management of patients with mild COPD.

Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: A comparison with patients with moderate-to-severe COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly incapacitating disease.^{1,2} Patients with mild COPD already present impairments in quadriceps muscle strength, health-related quality of life (HRQOL) and physical activity levels,^{3,4} that tend to worsen over time.⁴ Pulmonary rehabilitation (PR) is effective in improving dyspnea and HRQOL,⁵ and it is recognized as a core component of the management of patients with moderate-to-severe COPD.⁶ In patients with mild COPD, however, the disease-modifying potential of PR is not yet established. This has been identified by the 2013 American Thoracic Society/European Respiratory Society official statement on PR as a major research topic to be addressed.⁶ From the studies available, PR appears to improve exercise tolerance and HRQOL of patients with mild COPD.^{7,8} Nevertheless, these studies were only focused on the short-term effects of PR.⁹ Long-term studies are needed to determine the effectiveness of PR in this group of patients. In patients with moderate-to-severe COPD, it has been shown that in the absence of any maintenance strategy, benefits of PR diminish over 6-12 months.¹⁰ Reasons for this decline are multifactorial, comprising decreased adherence to exercise, progression of the disease and exacerbations.^{11,12} Patients with mild COPD may benefit equally from PR and its benefits may also decrease over time. However, this has not yet been explored. Thus, this study investigated the short- and long-term effects of PR in patients with mild COPD in comparison with patients with moderate-to-severe COPD.

Methods

Design and Participants

A non-experimental, prospective two-arm longitudinal study was conducted. Outpatients with COPD were recruited from two community primary care centers. Inclusion criteria were diagnosis of mild, moderate or severe COPD,¹³ age ≥40 years old, and clinical stability (i.e., 1 month without hospital admissions or exacerbations).¹³ Patients were excluded if they presented severe psychiatric, neurologic or musculoskeletal conditions¹⁴ and/or unstable

cardiovascular disease that could interfere with their performance during exercise training. The study was approved by the Center Health Regional Administration and from the National Data Protection Committee. Eligible patients, identified via clinicians, were contacted by the researchers, who explained the purpose of the study. Written informed consent was obtained prior to data collection.

Intervention

A 12-week PR program was delivered in a community primary-care center by three physical therapists. This program, described in detail elsewhere, was composed of 3 weekly sessions of exercise training (60 min) and 1 weekly session of psychoeducation (90 min).⁸ Each session of exercise training comprised of five components: warm up, endurance training, strength training, balance training and cool down. Patients with mild and with moderate-to-severe COPD trained together, which ensured a uniform training. In addition, it enabled the sharing of experiences among patients with different disease severities. At the end of PR, all patients were advised to continue exercising at home.

Data Collection

Socio-demographic, anthropometric and clinical data were first obtained. Spirometry (MicroLab 3500, CareFusion, Kent, UK) was then performed.¹⁵ Patients were classified using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) combined assessment (Modified Medical Research Council questionnaire (mMRC), spirometric classification and history of exacerbations in the previous year).¹³ Exercise tolerance, dyspnea, self-reported physical activity, history of exacerbations, HRQOL and peripheral muscle strength were assessed in a standardized order at baseline (pre-PR), and 3 (post-PR), 6 and 9 months later.

Feasibility measures

Feasibility was assessed by adherence to PR sessions, number/reasons of dropouts and number of adverse events.

Outcome Measures

Primary outcome

Exercise tolerance was measured using the 6-min walk test (6MWT). The measurement properties of this test are well established in COPD.¹⁶ Two tests were performed according to

international guidelines¹⁷ and the best performance was considered. The minimal important difference for the 6MWT is 25 meters.¹⁸

Secondary outcomes

Dyspnea. Patients reported their activities limitation resulting from dyspnea by selecting one statement of the mMRC.¹³ The questionnaire comprises five grades (0-4), with higher grades indicating greater perceived respiratory limitation. Variations of 1 indicate a perceived clinical improvement.¹⁹

Peripheral muscle strength. Muscle strength of the major muscle groups of the chest, shoulders and thighs were determined by the 1 repetition maximum (1-RM)²⁰ in chest press and knee extension exercises (Multigym Plus G112X, Vitoria-Gasteiz, ES).

Self-reported physical activity. The brief physical activity assessment was used as it is reliable²¹ and recommended to assess physical activity in COPD.²² It consists of two questions (score 0-4) about the frequency and duration of vigorous/moderate intensity physical activity undertaken in a “usual” week.²¹ The total score is obtained from the sum of the two questions. Score < 3 means that patient is insufficiently active and ≥ 4 that is sufficiently active.²¹

History of exacerbations. Patients were asked about the number of exacerbations in the preceding 3 months.^{23,24} Patients were explained what was an exacerbation using the current standardized definition.²⁵

Health-related quality of life. The St George Respiratory Questionnaire (SGRQ) was used.²⁶ The questionnaire has three domains: symptoms, activities and impact. The SGRQ presented high internal consistency with Cronbach's alphas of .770 in the symptoms domain, .740 in the activities domain, .634 in the impact domain and of .830 in the overall questionnaire. Score ranges from 0 (no impairment) to 100 (maximum impairment). A change of 4 units is considered clinically relevant.²⁶

Statistical Analysis

Using G*Power 3.1 (University Düsseldorf, Düsseldorf, DE), it was determined that 19 patients with mild COPD were required to yield 95% power ($\alpha=0.05$) to detect a statistically significant difference in 6MWT using an effect size of 0.88.⁷ However, 40 patients were recruited to increase the power to detect changes in the secondary outcome measures and to

compensate for the 20-40% expected dropouts.^{27,28} The same number of patients with moderate-to-severe COPD was recruited.

Descriptive statistics were used to describe the sample. Differences i) between completers and dropouts in each group at each time point, and ii) between patients with mild and moderate-to-severe COPD at baseline were tested using independent t-tests for continuous normally distributed data, Mann-Whitney U tests for continuous non-normally distributed data and chi-square tests for categorical data.

Two-way analysis of variance with repeated measures was used to establish the significant effects of time, group and these factors in combination.²⁹ The effect size was computed via Partial eta-squared as it is the index more commonly reported in the analysis of variance.³⁰ Partial eta-squared (η^2) was interpreted as small (≥ 0.01), medium (≥ 0.06) or large (≥ 0.14).³¹ When the effect of time was significant, post hoc analyzes were conducted with pairwise comparisons using the Bonferroni correction. When the effect of group was significant, a one-way analysis of variance with repeated-measures and pairwise comparisons using Bonferroni correction were performed.

Statistical analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and plots created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

Results

Participants

A total of 61 completed the study (Figure 1).

[Figure 1]

For each group, there were no significant differences between completers and dropouts at any time point ($p>0.05$). Participants from both groups were similar at baseline, with the exception of lung function, GOLD combined assessment, physical activity and SGRQ ($p<0.05$) (Table 1). None of the patients used long-term oxygen therapy or needed supplemental oxygen during exercise training.

[table 1]

Feasibility

No significant differences between groups were observed in exercise training (mild 80±11% vs moderate-to-severe 76±14%, $p=0.226$) or psychoeducation (mild 90±13% vs moderate-to-severe 92±9%, $p=0.439$) adherence. Dropouts were similar in both groups, with rates of 20 and 27.5% ($p=0.300$). No adverse events were reported.

Primary outcome

Figure 2 summarizes the results of the 6MWT over the 4 time points. There was no effect for group ($p=0.170$) nor significant interaction between time and group ($p=0.883$), but a significant effect for time was found ($p<0.001$; $\eta^2=0.419$). Exercise tolerance increased significantly immediately after PR ($p<0.001$), with most participants achieving a clinical meaningful improvement (mild 68.8%, moderate-to-severe 70.4%, $p=0.560$) (Table 2). These improvements were maintained at 6 and 9 months (Figure 2, Table 3).

[Figure 2, tables 2/3]

Secondary outcomes

For all secondary outcomes, the interaction between time and group was not significant ($p>0.05$), with the exception of history of exacerbations ($p=0.029$). mMRC showed an effect for time ($p=0.001$; $\eta^2=0.090$) and for group ($p=0.005$; $\eta^2=0.135$). Post hoc analysis revealed that mMRC changed significantly in participants with mild COPD across time ($p<0.001$; $\eta^2=0.184$). In this group, dyspnea decreased after PR (MD 0.6; $p<0.001$) (Table 2), but at 6 (MD=-0.3, $p=0.006$) and 9 (MD=-0.4, $p=0.003$) months this improvement was not sustained (Table 3). No significant differences in mMRC were observed in participants with moderate-to-severe COPD ($p=0.205$).

Significant differences were found over time for the chest press, knee extension and physical activity (p from <0.001 to 0.029 ; η^2 from 0.1 to 0.463), nevertheless, there were no differences between groups ($p>0.05$). These improvements were observed after PR (p from <0.001 to 0.010 , Table 2) and sustained at 6 and 9 months for physical activity, but not for chest press (all $p<0.002$) and knee extension (all $p<0.001$) (Table 3). The number of exacerbations significantly decreased from baseline to 6 months in both groups ($p=0.001$). At 6 and 9 months, the number of exacerbations was not significantly different from the number observed after PR. However, the significant interaction found ($p=0.029$), showed that participants with moderate-to-severe COPD had a higher reduction in the number of exacerbations (Table 3).

For the SGRQ total and domains scores, there was a significant difference between groups (p from <0.001 to 0.002 ; η^2 from 0.161 to 0.236) and over time (p from <0.001 to 0.016 ; η^2 from 0.061 to 0.304). Figure 3a shows the SGRQ total score over time. After PR, the magnitude of improvement in SGRQ total score was greater in participants with moderate-to-severe COPD ($MD=8.5$; $p=0.006$) than the improvement in participants with mild COPD ($MD=5.8$; $p=0.016$) (Table 2). Nevertheless, most participants achieved a clinically meaningful improvement, with no differences between groups (mild 65.6% and moderate-to-severe 77.8%; $p=0.392$). In the symptoms domain, both groups improved from baseline to post-PR ($p=0.013$ and $p=0.003$), but participants with mild COPD had a further improvement from post-PR to 9 months ($p=0.002$) (Figure 3b). Improvements in the activity domain were observed in both groups, however, they were greater in participants with moderate-to-severe COPD than in those with mild COPD ($\eta^2=0.196$ vs. $\eta^2=0.106$) (Figure 3c). Improvements in the impact domain were only seen in participants with moderate-to-severe COPD ($p=0.010$; $\eta^2=0.144$) (Figure 3d). The benefits of PR in SGRQ total and domains scores were sustained at 6 and 9 months in both groups (Table 3).

[Figure 3]

Discussion

This was the first study to assess the short- and long-term effects of PR in patients with mild COPD in comparison with patients with moderate-to-severe COPD. The main findings suggest that PR is effective in improving exercise tolerance, peripheral muscle strength, physical activity, HRQOL and in reducing the number of exacerbations in patients with mild COPD as well as in patients with moderate-to-severe COPD. Moreover, most of the achieved benefits were maintained at 9 month follow-up. The magnitude of the benefits were substantial and similar to other interventions (smoking cessation,³² pharmacological interventions^{33,34}) that are recommended for mild COPD. In addition, it was found that PR is as feasible for mild COPD as for moderate-to-severe disease.

The 6MWT improvement in patients with mild COPD was similar to that found in patients with moderate-to-severe COPD and it is in line with the range of values found in previous studies (34-60 meters).³⁵⁻³⁷ Moreover, the increase was above the established minimal clinically important difference for the 6MWT.¹⁸ Nevertheless, exercise tolerance tended to

decrease from post-PR to the end of the follow-up period in both groups.^{11,36} The decline in the 6MWT raises the question of whether there are strategies that could promote longer lasting improvements (e.g., maintenance programs, telephone follow-up; feedback on physical activity levels). A recent study demonstrated that benefits of PR could be maintained in patients with moderate-to-severe COPD up to 1-year with a community-based maintenance exercise program supervised by fitness instructors.³⁵ This approach may also be feasible for patients with mild COPD and thus it should be explored in future research.

Dyspnea improved significantly with PR,¹⁹ yet this benefit was not observed in patients with moderate-to-severe COPD, contradicting earlier studies.^{35,38} These differences may be due to the properties of the instruments used. In the present study, dyspnea was assessed with the mMRC, whereas in previous literature the Chronic Respiratory Disease Questionnaire (CRQ) was used.^{35,38} The mMRC, due to its limited number of levels, may have not been sensitive enough to detect small changes in patients with more advanced grades of the disease.³⁹ The CRQ, however, allows the symptoms to be expressed in a graduated scale,⁴⁰ which may be more adequate to detect small changes. Future studies could investigate the sensitivity of the CRQ dyspnea domain to assess the impact of PR in mild COPD.

In line with previous studies,^{41,42} PR resulted in improvements in peripheral muscle strength. But after the initial improvement, losses similar to those described in the literature were observed.³⁸ Compared to baseline, at 3, 6 and 9 months, the percentage of patients sufficiently active increased (from 11-38% to 56-82%). However, care must be taken when interpreting this finding as patients' estimations of time spent in physical activities have been shown to be inaccurate compared with objective quantification (e.g., motion sensors).⁴³ Nevertheless, in the present study, the brief physical activity assessment was used and it has been demonstrated that simple questionnaires, with an interval response option, have high coefficients of reliability and validity.⁴⁴ Moreover, subjective methods have practical value mainly in providing the patients' view on their performance in activities of daily living.⁴⁵ Thus, the self-reported improvements in physical activity, even if not reflecting a true change, may reflect the importance of PR for increasing patients' awareness of their physical activity levels. A decline in number of exacerbations after PR was also found, which was sustained at 9 months. Nonetheless, this benefit was more marked in patients with moderate-to-severe COPD.^{23,24}

The improvement in SGRQ exceeded the established minimal important difference and was sustained at 9 month follow-up.²⁶ Previous studies in patients with moderate-to-very-severe COPD reported similar results.^{11,36,37,46} In addition, from post-PR to 9 month follow-up, SGRQ symptoms domain continued to improve in patients with mild COPD, sustaining the clinical relevance.

The overall findings suggest that PR conducted in the community is beneficial for patients with mild COPD. According to a clinical practice guideline, PR should be prescribed for symptomatic individuals with a FEV₁<50% predicted, and could be considered for symptomatic or exercise-limited individuals with a FEV₁ ≥50% predicted.⁴⁷ The present study shows, however, that patients with mild COPD benefit from PR. Thus, despite the relevance of FEV₁ in diagnosing COPD, it may be valuable to rethink the inclusion of FEV₁ as a criterion for PR selection. Furthermore, the high adherence showed that PR was feasible and well tolerated in this group of patients. Community-based programs could be a novel approach to deliver PR to patients with mild COPD at a modest cost and using the existing community resources. Future research should assess the cost-effectiveness of this approach compared to standard care prior to broader implementation. Nevertheless, results also demonstrate that, similarly to what happens with patients with moderate-to-severe COPD, the benefits in patients with mild COPD start to decline after PR. This finding therefore points out to the importance of keeping patients motivated in changing behaviors after the program to maintain benefits. In patients with moderate-to-severe COPD, the benefits of PR have been shown to be maintained for up to 1-year with a community-based maintenance exercise program, with minimal supervision from trained fitness instructors.³⁵ This method may also be effective in sustaining benefits in mild COPD and should be investigated in future research.

Some limitations need to be acknowledged. The absence of a control group is a limitation of this study. Inclusion of a group of patients with mild COPD receiving standard care would have strengthened the findings. Outcome assessment was also not blinded. Evaluators were the same physical therapists that delivered the program. Nevertheless, to minimize bias, the encouragement given by evaluators was standardized. This study had a follow-up period of 9 months. To assess the potential of PR to modify the disease trajectory in mild COPD, studies with longer follow-ups are recommended.

Conclusions

PR is effective in patients with mild COPD as well as in patients with moderate-to-severe COPD. Moreover, most of the achieved benefits were maintained at 9 month follow-up. These data suggest that PR could be part of the management of mild COPD. Further work is warranted to determine the potential of PR to modify the disease trajectory in patients with mild COPD prior to a broader implementation.

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1 Table 1. Characteristics of the participants at baseline

Characteristics	Mild COPD (n=32)	Moderate-to-severe COPD (n=29)	p-value
Age (yrs)	65.9 ± 8.9	65.5 ± 9.8	.853
Male	22 (68.8%)	24 (82.8%)	.113
BMI (kg/m ²)	28.4 ± 4.6	29.6 ± 4.5	.347
Smoking status			
Current smokers	12 (37.5%)	7 (24.1%)	.109
Former smokers	16 (50%)	13 (44.8%)	.887
Never smokers	4 (12.5%)	9 (31.1%)	.054
FEV ₁ (L)	2.2 ± 0.5	1.5 ± 0.5	<.001
FEV ₁ (% predicted)	86.7 ± 5.2	55.4 ± 16.7	<.001
FEV ₁ /FVC (%)	66.4±6.0	58.9±11.9	.002
GOLD combined assessment			
A – low risk, less symptoms	23 (71.9%)	9 (31%)	.002
B – low risk, more symptoms	6 (18.8%)	4 (13.8%)	
C – high risk, less symptoms	1 (3.1%)	9 (31%)	
D – high risk, more symptoms	2 (6.2%)	7 (24.2%)	
6MWT	473.5 ± 73.3	447.6 ± 80.8	.202
mMRC	1.3 ± 0.9	1.6 ± 0.8	.105
Chest press (kg)	31.9 ± 10.5	31.6 ± 9.6	.917
Knee extension (kg)	41.6 ± 15.7	39.9 ± 9.4	.653
Physical activity	2.4 ± 2.1	1.1 ± 1.4	.009
Exacerbations past 3 months	0.8 ± 1.3	1.6 ± 1.6	.051
SGRQ total	28.0 ± 16.9	45.2 ± 16.4	<.001
SGRQ symptoms	41.3 ± 21.4	55.0 ± 19.2	.013
SGRQ activities	41.1 ± 22.8	59.8 ± 15.5	.001
SGRQ impact	16.3 ± 14.7	33.9 ± 19.7	<.001

- 1 Data are presented as mean±SD or n(%). Abbreviations: BMI, body mass index; FEV₁, forced
2 expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic
3 Obstructive Lung Disease; 6MWT, 6-min walk test; mMRC, Modified Medical Research Council
4 questionnaire; SGRQ, St George Respiratory Questionnaire.

Table 2. Mean differences between baseline and 3 month follow-up (post-pulmonary rehabilitation).

Outcome	Mean difference (baseline to 3 months)	
	Mild	Moderate-to-severe
6MWD	-52.8 (-68.8→-36.8)	-49.7 (-64.5→-34.9)
mMRC	0.6 (0.3→0.9)	0.1 (-0.2→0.5)
Chest press (kg)	-10.0 (-13.2→-6.7)	-11.1 (-13.7→-8.5)
Knee extension (kg)	-18.5 (-24.9→-12.1)	-17.1 (-21.4→-12.8)
Physical activity	-2.2 (-3.2→-1.2)	-3.5 (-4.3→-2.7)
Exacerbations past	0.4 (0.1→0.7)	0.8 (0.2→1.4)
3 months		
SGRQ total	5.8 (2.2→9.5)	8.5 (3.9→13.0)
SGRQ symptoms	7.6 (1.7→13.4)	11.1 (4.0→18.2)
SGRQ activities	10.0 (3.4→16.5)	8.9 (2.5→15.3)
SGRQ impact	2.8 (-0.6→6.2)	7.4 (1.8→12.9)

Data are presented as mean difference (95% confidence intervals). Abbreviations: 6MWD, 6-min walk distance; mMRC, Modified Medical Research Council questionnaire; PR, pulmonary rehabilitation; SGRQ, St George Respiratory Questionnaire.

Table 3. Mean differences between the 3 month follow-up (post-pulmonary rehabilitation) and the 6 and 9 month follow-ups.

Outcome	Mean difference (3 months to 6 months)		Mean difference (3 months to 9 months)	
	Mild	Moderate-to-severe	Mild	Moderate-to-severe
6MWD	8.6 (-2.8→20.0)	2.3 (-13.4→18.1)	13.2 (2.9→23.6)	14.1 (-1.9→30.1)
mMRC	-0.3 (-0.6→-0.1)	0.1 (-0.2→0.4)	-0.4 (-0.7→-0.1)	0.1 (-0.2→0.4)
Chest press (kg)	3.6 (0.4→6.7)	3.2 (0.9→5.6)	5.3 (2.7→7.9)	5.4 (2.7→8.2)
Knee extension (kg)	4.5 (0.5→8.4)	7.9 (4.2→11.5)	9.9 (4.9→15.0)	10.7 (6.4→15.0)
Physical activity	1.0 (0.1→1.9)	1.0 (0.0→1.9)	0.4 (-0.4→1.3)	0.3 (-0.8→1.4)
Exacerbations past 3 months	0.0 (-0.3→0.3)	0.1 (-0.3→0.5)	-0.3 (-0.7→0.2)	0.2 (-0.2→0.6)
SGRQ total	2.0 (-1.1→5.0)	2.8 (-2.1→7.7)	4.5 (0.5→8.5)	3.3 (-1.1→7.6)
SGRQ symptoms	6.9 (-1.2→15.0)	-0.6 (-8.8→7.5)	14.0 (5.6→22.4)	3.3 (-5.4→11.9)
SGRQ activities	3.4 (-6.9→13.6)	10.9 (0.1→21.7)	-0.4 (-6.4→5.5)	2.9 (-2.5→8.3)
SGRQ impact	-1.4 (-5.9→3.2)	4.6 (-4.7→14.0)	-2.4 (-8.2→3.4)	3.7 (-0.8→8.1)

Data are presented as mean difference (95% confidence intervals). Abbreviations: 6MWD, 6-min walk distance; mMRC, Modified Medical Research Council questionnaire; PR, pulmonary rehabilitation; SGRQ, St George Respiratory Questionnaire.

Figure legends

Figure 1 - Participant flow diagram throughout the study.

Figure 2 - 6-min walking distance from baseline to 9 month follow-up in patients with mild COPD and patients with moderate-to-severe COPD. Data are presented as mean and standard error. * p<0.001 from baseline to post pulmonary rehabilitation.

Figure 3 - St George Respiratory Questionnaire total (a) and domain (b, c, d) scores from baseline to 9 month follow-up in patients with mild COPD and patients with moderate-to-severe COPD. Data are presented as mean and standard error. * p<0.001 from baseline to post pulmonary rehabilitation, # p=0.002 from post pulmonary rehabilitation to 6 months.

Figure 2

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Figure 3

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22nd October 2015

Dear Professor Larry F. Hamm,

Please find enclosed an original article entitled "Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: a comparison with patients with moderate-to-severe COPD" by Cristina Jácome and Alda Marques for peer review for *Journal of Cardiopulmonary Rehabilitation and Prevention*.

It is well established that pulmonary rehabilitation (PR) is effective in improving dyspnea and health-related quality of life of patients with moderate-to-very-severe COPD. However, the effects of PR in patients with mild COPD have not yet been established. Thus, this study investigated the short- and long-term effects of PR in subjects with mild COPD in comparison with subjects with moderate-to-severe disease. The overall findings show that PR improves exercise tolerance, muscle strength, physical activity and health-related quality of life and reduces exacerbations in subjects with mild COPD as in subjects with moderate-to-severe COPD, and that most of these benefits last for at least 6 months. This study is a relevant step towards the integration of PR as part of the management of patients with mild COPD.

This work was supported by Portuguese National Funds through FCT - Foundation for Science and Technology [grant number SFRH/BD/84665/2012], however, I declare that the authors have not entered into an agreement with the funding organization that has limited their ability to complete the research as planned.

All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language except as an abstract. I declare that they have no conflicts of interest.

We look forward to your response.

Yours Sincerely,

Alda Marques