

What still prevents to acknowledge a major role for pulmonary rehabilitation in COPD treatment?

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Summary. Chronic obstructive pulmonary disease (COPD) is a major health issue, particularly in aging people. Despite an increasing availability of drugs to treat COPD, recent data indicate that an actual control of the disease is achieved in a minority of patients. This makes apparent that additional treatments of COPD should be taken into account, such as pulmonary rehabilitation (PR), which was introduced in the 1960s and has large evidence of clinical effectiveness. PR is a non-pharmacologic therapy based on a comprehensive, multidisciplinary, patient-centered intervention comprising exercise training, self-management education and psychosocial support. PR treated patients develop an increased exercise tolerance and quality of life, reduced dyspnea and anxiety, and are concerned by less hospital admissions for disease exacerbations. Notwithstanding, the use of PR in COPD patients is negligible, being globally estimated in 2-5%. Here we update the evidence in favor of PR and the actual need to consider it as a treatment to be considered for COPD patients with significant impairment in daily living activities. (www.actabiomedica.it)

Key words: COPD, drug treatment, pulmonary rehabilitation, effectiveness, exercise tolerance, dyspnea, quality of life

Introduction

Chronic obstructive pulmonary disease (COPD), as defined by the updated Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines “is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitations that are due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” (1). COPD is a significant burden to patients, particularly aging people, and society, that is especially associated to dyspnea, with an increasing impairment on daily living activities and quality of live resulting from the disease progress, and a mortality estimated in more than 3 million people worldwide per year (2). In front of an increasing availability of drugs to treat COPD,

according to a recent review “Current therapies provide only limited short-term benefit and fail to halt progression” (3). Actually, the two pivotal studies Toward a Revolution in COPD Health (TORCH) (4) and Understanding Potential Long-term Impacts on Function and Tiotropium (UPLIFT) (5) had a limited success. Namely, though both treatments decreased exacerbations and hospitalization rates, the salmeterol and fluticasone combination reduced over 3 years, compared to placebo, the decline in lung function but not the all cause mortality, while the treatment with tiotropium over 4 years did not significantly slow the decline in lung function, while reducing mortality (6). In a recent survey on 3672 COPD patients from US and Europe under a standard of care drug treatment, more than 80% reported to experience at least one symptom “often”, and 70% of patients reported some

level of non-adherence (7). Thus, it is apparent that additional treatments of COPD should be taken into account. Among these, pulmonary rehabilitation (PR), which was introduced in the 1960s, has large evidence of clinical benefit (8). In presenting PR to family physicians, Nici et al. defined it as a “nonpharmacologic therapy that has emerged as a standard of care for patients with COPD” that is based on a comprehensive, multidisciplinary, patient-centered intervention comprising exercise training, self-management education and psychosocial support, and resulting in an increased exercise tolerance, reduced dyspnea and anxiety, reduced hospital admissions for disease exacerbations, and improvement in health-related quality of life (HRQoL (9). Despite such background, the number of COPD patients undergoing PR is negligible, being globally estimated in 2-5% (10). For example, in US the analysis of data for Medicare beneficiaries with COPD who received PR from January 1, 2003, to December 31, 2012, showed that patients receiving PR increased from 2.6% in 2003 to 3.7% in 2012, but the improved use of PR was attributed to prior users more than new users of PR (11). It is not rare that less than 1% of COPD patients undergo PR each year, as reported for example from New Zealand, where this low rate of participation occurred even though PR was provided in 19 of 21 District Health Boards regions (12).

Here we update the evidence in favor of PR and the actual need to consider it as a treatment to be performed in COPD patients with impairment in daily living activities

Evidence of PR effectiveness as assessed by meta-analyses

The highest grade of scientific evidence for medical treatments is provided by positive systematic reviews and meta-analyses. The first meta-analysis on randomized controlled trials of PR (with control groups receiving no rehabilitation), in patients with COPD was performed in 1996. Significant improvements were found for all the outcomes, though dyspnea and better control over COPD were mentioned as clinically important, while the value of the improvement in exercise capacity was not clear (13). From 2002 to 2015 three Cochrane meta-analyses were published. Their main data are summarized in table 1. Actually, the first meta-analysis reanalyzed by the Cochrane database systematic review methods the same trials previously assessed, with similar conclusion but a final statement mentioning that “Rehabilitation forms an important component of the management of COPD” (14). In the 2006 meta-analysis, adding 8 further trials, the conclusion were that “Rehabilitation relieves dyspnea and fatigue, improves emotional function and enhances patients’ sense of control over their condition”, with the same final statement reported above (15). The 2015 meta-analysis, based on 65 trials, due the further confirmation of the positive outcomes, has lead the authors to write “It is our opinion that additional RCTs comparing pulmonary rehabilitation and conventional care in COPD are not warranted”. Indeed, because some studies included in the analysis addressed community-based programs, the authors

Table 1. Main data from Cochrane meta-analyses on pulmonary rehabilitation in COPD

Author, year [ref]	Number of trials included in the analysis	Weighted mean difference
Lacasse et al, 2002 [13]	23	Dyspnea score: 0.98 units, 95% Confidence Interval (95% CI) 0.74 - 1.22 units; n=9 trials. 6- minute walking distance: 49 m, 95% CI: 26 - 72 m; n=10 trials.
Lacasse et al. 2006 [14]	31	Dyspnea score: 1.0 units; 95% confidence interval: 0.8 to 1.3 units; n = 12 trials). 6-minute walking distance: 48 meters; 95% CI: 32 to 65; n = 16 trials).
McCarthy et al. 2015 [15]	65	Dyspnea: 0.79, 95% confidence interval (CI) 0.56 to 1.03; n = 19 trials 6-minute walking distance 43.93, 95% CI 32.64 to 55.21; n = 38 trials

suggested “Future research studies should focus on identifying which components of pulmonary rehabilitation are essential, its ideal length and location, the degree of supervision and intensity of training required and how long treatment effects persist (16). In fact, in 2014 a meta-analysis of 18 trials on home-based pulmonary rehabilitation programs was published, with data comparison between treated and untreated patients suggesting this kind of PR as an effective therapeutic intervention to relieve COPD-associated respiratory symptoms and improving HRQoL and exercise capacity (17). However, a recent meta-analysis compared hospital (outpatients) and home-based exercise training rehabilitation programs for COPD. Ten trials were analyzed, with low to moderate evidence that outpatient and home-based exercise training programs are equally effective (18). Therefore, the suitability to apply home-based PR with an expected outcome comparable to outpatients programs needs to be investigated by large-scale controlled trials to identify the most favorable standard program (17).

Another issue in search of elucidation is the effectiveness of PR in patients with mild COPD. Two meta-analyses are available. The authors of the first meta-analysis, including 3 studies with different designs (retrospective, one group pretest-posttest, and randomized controlled trial) concluded that most of the PR programs had positive effects on exercise capacity and HRQoL in patients with mild COPD, but the evidence was insufficient and studies with robust designs and with longer follow-up should be conducted (19). The second meta-analysis, including 4 randomized controlled trials, found a clinically and statistically significant improvement in short-term HRQoL, but not at the follow-up. There was an improvement in the 6-minute walk test with PR, though not considered clinically relevant. The data for muscle strength and maximal exercise capacity were insufficient for meta-analysis (20).

Also the capacity of PR to reduce COPD exacerbations was evaluated in three Cochrane meta-analyses. The first included 6 trials and showed that PR significantly decreased hospital admissions (odds ratio 0.13 (95% CI 0.04 to 0.35)), number needed to treat (NNT) 3 (95% CI 2 to 4) over 34 weeks, and mortality (odds ratio 0.29 (95% CI 0.10 to 0.84), NNT 6

(95% CI 5 to 30) over 107 weeks) (21). In the 2011 update, 9 trials were analyzed, the figures confirming the significant reduction of hospital admissions (odds ratio 0.22 (95% CI 0.08 to 0.58)), NNT 4 (95% CI 3 to 8) over 25 weeks) and mortality (OR 0.28; 95% CI 0.10 to 0.84), NNT 6 (95% CI 5 to 30) over 107 weeks) (22). In the latest meta-analysis the number of selected studies was more than doubled, but the PR programs used in the 20 studies showed large variety in terms of exercise training (type, intensity and supervision), patient education (from none to extensive self-management programs) and kind of organization (one setting or various settings, e.g. hospital, outpatient centre and home). Such heterogeneity prevented to reach firm conclusions on the PR effects on hospital readmissions and mortality, and the authors claimed future research on the influence of PR programs in terms of exercise sessions, self-management education and other components affecting the outcomes (23).

Issues to be highlighted

Effects of PR on pulmonary function

Most studies on effectiveness of PR in COPD focused the interest on the improvement of HRQoL and physical performance and reduction of dyspnea, while pulmonary function, although obviously related to bronchial obstruction, was rarely included as a measure of efficacy. Stav et al. assessed the efficacy of a 3 year outpatient PR program in 80 patients with moderate to severe COPD, measuring pulmonary function and exercise capability, at 6, 12, 18, 24, 30, and 36 months. The control group received standard care only. The decline in forced expiratory volume in 1 second (FEV1) after the 3 years was significantly lower in the PR group compared to control, corresponding to 74 ml versus 149 ml ($p < 0.001$), and maximal sustained work and endurance time improved early and was maintained all over the study with PR, but not in the control group (24). In the study named FEV1 as an Index of Rehabilitation Success over Time (FIRST), the effects of PR on lung function were evaluated in 257 COPD patients treated with inhaled corticosteroids or long-acting β_2 -agonists and/or tiotropium during a 3-year duration of

PR, compared with 67 patients treated only with drugs. Lung function was measured at baseline and at one-year intervals. In the PR group, FEV1 increased from 1240 mL (57.3% of predicted value) to 1252.4 mL (60.8%) after 3 years, whereas in the controls the values were 1367 mL (55% of predicted) at baseline and 1150 mL (51%) after 3 years ($p < 0.001$) (25). The authors claimed for confirmation of such outcome from randomized trials. However, thus far only in the meta-analysis on randomized controlled trials of home-based PR for COPD patients pulmonary function (measured by FEV1/forced vital capacity) was found to be significantly better ($p < 0.0001$) after 12 weeks of intervention compared with the nonintervention control group (17). Another pulmonary function index is tidal volume, that in an analysis of three studies, which were based on training at high intensity (70%–80% maximum workload) in PR treated patients with moderate to severe stable COPD, was significantly improved in patients with reduced dyspnea (26).

Outcome of PR according to the severity of COPD

An impact of COPD severity on the clinical success of PR would be of obvious importance. In a study on 167 COPD patients undergoing PR, each subject was classified into one of 4 categories A, B, C, and D, according to exercise capacity, respiratory symptoms and health status. The groups were homogeneous in age, body mass index, smoking pack-years, and comorbidities. Significant improvements in all outcomes were detected, with categories A and C showing a more pronounced improvement in exercise capacity and symptoms. However, despite these differences, the likelihood to have a minimum clinically important difference in each outcome was similar for all categories when compared (27). Another study prospectively compared the benefit obtained by PR in 229 COPD patients according to baseline disease burden. Subjects were divided into 4 quartiles by their baseline level of dyspnea, FEV1 percent predicted and 6-minute-walk distance, with change in HRQoL (as assessed by the SF-36 questionnaire) being the primary outcome. After PR, clinically significant improvements were observed in most components of SF-36, particularly concerning physical function, health perception, physical

role, emotional role, social function, mental health, pain, vitality, and depression. The authors concluded that PR results in significant improvement in quality of life, dyspnea, and functional capacity irrespective of baseline disease burden (28). A similar improvement was shown using the SF-36 questionnaire in 440 patients treated with PR, of whom 229 completed the program. Of interest, patients completing PR had greater pain and depression score to the SF-36, and lower FEV1, and included a lower proportion of current smokers, while cigarette smoking was the sole independent predictor of PR dropout (29).

Cost-effectiveness of PR

Early economic evaluations of PR were limited to the cost. For example, in 1997 a study considered 46 stable COPD patients undergoing a PR program in 10 sessions including education, training, group therapy, and an individualized regimen of home-based extremity and inspiratory muscle exercise. The program resulted in significant decrease of dyspnea and significant increases of exercise capacity and forced vital capacity, with a cost of the 10 outpatient sessions of \$650 (30). Golmohammadi et al. calculated that the total direct cost per 100 person-years of follow-up before the program was \$122,071 while after the program it was \$87,704, with an average reduction of total costs of \$34,367 per 100 person-years, corresponding to \$344 per person per year ($p = 0.02$). Such reduction resulted from decreased health service utilization, reduced direct costs and improved health status of COPD patients treated with PR (31). Subsequent studies analyzed the economic benefit produced by the reduced hospital utilization and health cost (32, 33), while Griffiths et al. were the first to use the modern tool for cost-effectiveness analysis, specifically the quality adjusted life years (QALYs), that is a measure of disease burden, including both the quality and the quantity of life lived (34). The cost/utility analysis was performed along a randomized controlled clinical trial of PR vs. standard care in 200 patients randomly assigned to either an 18 visit, 6 week rehabilitation program or standard medical care. The difference between the mean cost of 12 months of care for patients in PR and control group was calculated. The results showed that each PR program for up to 20

patients cost £12,120, with a mean incremental cost of adding PR to standard care of -£152 (95% CI -881 to 577) per patient ($p=NS$). The incremental utility of adding PR was 0.030 (95% CI 0.002 to 0.058) QALYs per patient ($p=0.03$). Thus, the outpatient PR program produced cost per QALY ratios within limits considered to be cost effective and likely to result in financial benefits to the health service (35). In another study from UK, also the cost effectiveness of maintenance schedules following initial PR was investigated in COPD patients who completed at least 60% of a standard 8-week PR program and were randomized to a 2-h maintenance session at 3, 6 and 9 months (73 subjects) or treatment as usual (75 subjects). QALYs and incremental cost-effectiveness ratio (ICER) were used. At 12 months, incremental cost to the NHS and social services was -£204.04 (95 % CI -£1522 to £1114), and QALY gains were -0.007 (-0.461 to 0.447) and +0.015 (-0.050 to 0.079). Based on point estimates, PR maintenance therefore was dominant over usual treatment from the perspective of the NHS and social services. A need of future research to evaluate whether also more intensive PR maintenance regimens offer benefit to patients at reasonable cost was suggested (36). Recently, Atsou et al. estimated the effectiveness and cost-effectiveness of PR in a hypothetical cohort of COPD patients in France using a multi-state Markov model adopting society's perspective. Simulated cohorts of COPD patients in GOLD stage 2 to 4 with and without PR were compared in terms of life expectancy, QALYs, disease-related costs, and ICER. At the horizon of a COPD patient's remaining lifetime, PR would result in mean gain of 0.8 QALY, with an over disease-related costs of 14,102 € per patient. The ICER was 17 583 €/QALY. Sensitivity analysis showed that PR was cost-effective in every scenario (ICER <50 000 €/QALY). According to authors, these outcomes should provide a useful basis for COPD PR programs (37).

Conclusions

In 2006, the American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation concluded the analysis of the available literature with the assertion "A considerable body of

theoretical and practical knowledge has already been developed, resulting in the establishment of pulmonary rehabilitation as a science. We look forward to refining its process, improving its efficiency, optimizing its benefits, and expanding its scope" (38). In fact, in the 2013 updated document the conclusion was "The considerable growth in the science and application of pulmonary rehabilitation since 2006 adds further support for its efficacy in a wide range of individuals with chronic respiratory disease" (39). This highlights that also respiratory chronic disorders different from COPD should be treated with PR. In front of this large evidence, PR remains greatly underestimated and underused. According to Troosters et al., "the future of pulmonary rehabilitation is bright", but requires engaging more patients in better tailored programmes, that need to be widely advertised, with healthcare professionals well trained to deal with the individual needs and preferences of patients. Also, patients need to develop self-management skills enabling them to maintain the benefits of the programme activity (40).

The latest document from the American Thoracic Society/European Respiratory Society, based on the demonstration of physiological, symptom-reducing, psychosocial, and health economic benefits achieved by PR, and of insufficient funding, resources and reimbursement, lack of healthcare professional, payer, and patient awareness and knowledge, was aimed at enhancing implementation, use, and delivery of PR to suitable individuals worldwide. This document contains policy recommendations to evolve healthcare professional, payer, and patient awareness and knowledge of PR, to increase patient access to PR and to ensure quality of PR programs. The ATS and ERS will undertake actions to improve access to and delivery of PR services for suitable patients, and call on their members and other health professional societies, payers, patients, and patient advocacy groups to join in this commitment (41).

We must hope that this initiative can finally succeed in making acknowledged the actual role of PR in COPD treatment.

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