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Determinants of success

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ABSTRACT: In chronic obstructive pulmonary disease (COPD) patients, pulmonary rehabilitation is a nonpharmacological intervention aimed at improving physical exercise tolerance, dyspnoea and perceived quality of life. However, identifying predictors of clinical response and which patients achieve benefit remains a difficult question to answer with no conclusive data available.

Baseline characteristics of COPD patients, such as degree of breathlessness, body weight and arterial partial pressure of oxygen, generally appear to be too direct to have a correlation with improvement of post-rehabilitation outcomes. Furthermore, some additional benefits of patients treated with rehabilitation are simply not detected by usual measures (social interaction, sleep quality and confidence).

Although there are some data suggesting that some medical conditions frequently associated with COPD (osteoporosis, metabolic syndrome and heart diseases) may negatively influence rehabilitation outcomes, at present the evidence is contradictory.

KEYWORDS: Attendance, chronic obstructive pulmonary disease, comorbidities, effectiveness, minimum clinically important difference, predictors, pulmonary rehabilitation

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Pulmonary rehabilitation is a nonpharmacological intervention, which is effective for chronic obstructive pulmonary disease (COPD) patients who complete, take part and engage. The treatment effect is large and benefits on exercise capacity, dyspnoea and quality of life consistently exceed the minimum clinically important difference (MCID) for these outcomes [1, 2]. However, determining who benefits most from pulmonary rehabilitation remains a difficult question.

In one clinical analysis of 91 subjects undertaking pulmonary rehabilitation, an evaluation of response was made after categorising response into dichotomous or composite measures of health status and/or exercise tolerance [3]. In this study, 37% of patients achieved benefits in both health status and exercise tolerance whereas 27% were nonresponders for both: 17% and 14%, respectively, showed improvements in health status or exercise tolerance only. Identifying predictors of response was difficult and no conclusive data were available. Although, in this study, patients with baseline breathlessness at Medical Research Council (MRC) level 5 (housebound by breathlessness) showed a smaller magnitude of improvement, in combination with other variables, this was not a significant predictor.

In another study examining response to pulmonary rehabilitation, the authors identified that patients who performed well with rehabilitation tended to be those who had more peripheral muscle weakness and less ventilatory limitation at the start of the programme compared with those who were stronger but more ventilatory impaired [4]. This compelling data makes clinical sense but is limited in application to rehabilitation services, particularly in the UK, where muscle strength is not routinely measured. Furthermore, these findings accounted for only a small percentage of the variance in response in patients with COPD.

In a more recent observational study aimed at defining the clinical predictors of pulmonary rehabilitation efficacy, comprehensive data was available on lung function parameters in 60 severe COPD patients and included in the regression analyses [5]. In this analysis patients were categorised according to the following baseline variables: pulmonary hyperinflation, body mass index (BMI), arterial oxygen tension (P_{a,O_2}) and severity of airflow obstruction. Whilst these baseline

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variables were unable to account for differences in change in quality of life after rehabilitation, there was evidence that patients with a BMI >25 kg·m^{-2} and greater initial hypoxaemia (P_{a,O_2} <60 mmHg) did better with respect to changes in 6-min walking distance (6MWD). This is an interesting and perhaps unexpected finding, although it does support earlier data, which suggest that hypoxic patients do well even when trained without additional oxygen [6]. However, confidence intervals for these findings were wide-ranging, reflecting the relatively small sample size. Furthermore, the relationship between baseline arterial oxygen and change in 6MWD, considered as a continuous, as opposed to dichotomised, variable, was nonsignificant and only suggestive of a relationship for BMI. In other studies, the physiological response of 6MWD has been shown to be similar between obese and nonobese COPD patients [7] and in one head-to-head comparison, obese patients performed as well with rehabilitation as nonobese patients [8].

ATTENDANCE

One important determinant of success may be attendance of rehabilitation sessions. In one study offering different frequencies of supervised sessions (once weekly *versus* twice weekly), attendance between the two groups was not different, although the once weekly groups attended for a longer period of time [9]. Outcomes between the two groups were similar, although health-related quality of life changes were smaller in the once weekly group. However, with a very small sample size, caution is required.

Many authors have considered the causes of nonattendance and drop-out in more detail; in the study by FISCHER *et al.* [10], 50 (23%) out of 217 patients did not complete the course. For ~50% of these, drop-out was explained by the illness itself, exacerbations, deterioration in symptoms or comorbidities. Those who dropped out for medical reasons were no different to those who dropped out for other reasons (*e.g.* limitations in social activities) [10]. In this study, drop-out was unexplained by any measured clinical or psychosocial variables; however, depression was not measured, which has previously been shown to be a predictor of drop-out [2].

When looking at causes of nonattendance during rehabilitation, FISCHER *et al.* [10] found that ~27% of causes were due to COPD or other comorbidities and 31% of absenteeism was unexplained. Using multiple regression techniques to compare high and poor attendance records, the authors found a combination of low fat-free mass and poor sense of control predicted poor attendance. Although continued smoking was higher in those with poor attendance, this was not significant in the regression analysis. Again, it should be highlighted that with relatively low-frequency ''events'', for example, poor attendance or drop-out, larger sample sizes are required to avoid spurious results. To what extent low fat-free mass reflects severity of illness and, as such, impacts on attendance remains unclear. Interestingly, distance and travel time to the sites did not appear to influence attendance. With average travel times of 20 min for both high and low attendees, this may be significantly greater in other countries and perhaps further complicated by parking restrictions, availability of public transport and hospital-provided transport.

PATIENT'S COMPLEXITY

Advanced COPD is frequently seen in association with other medical conditions, such as systemic hypertension, diabetes, coronary artery disease and heart failure. These comorbidities share pathophysiological mechanisms and influence patients' health [11, 12]. Indeed, somatic chronic comorbidities appear to have greater negative influence on the individual's decline in physical functions than expected [13]. In elderly people [14], comorbidities may negatively impact on the rehabilitation of patients, leading to smaller gains [15, 16].

This aspect has been further investigated in COPD patients. In a single-centre, retrospective analysis using a large sample size (n=2,962; mean age 71 yrs), the impact of single or aggregated comorbidities on outcomes associated with pulmonary rehabilitation was explored [17].

Authors have shown that some comorbidities can significantly influence discharge outcomes in patients who underwent a standard programme. In particular, the proportion of patients with a pre-defined improvement greater than the MCID in perceived breathlessness (-1 point on the modified MRC scale) [18, 19] and health-related quality of life (-4 points on the St George's Respiratory Questionnaire (SGRQ)) [20, 21] did not differ across categories of COPD patients with no, one or at least two comorbidities. In addition, the number and percentage of patients who clinically improved in exercise performance (54 m at 6MWD) [22] was not different according to the same comorbidity categories [17] (62, 59 and 62%, respectively). In a multiple logistic regression model, individuals' self-reported comorbidity score, as assessed by the index of CHARLSON *et al.* [23], and the presence of metabolic syndrome (systemic hypertension, diabetes and dyslipidaemia) were inversely related to improvement in 6MWD (OR 0.72 and 0.57, respectively) [17]. Moreover, heart diseases such as chronic heart failure and/or coronary heart disease directly and indirectly predicted the improvement in exercise tolerance (OR 2.36) and perceived quality of life (OR 0.67) [17].

VAGAGGINI *et al.* [5] showed similar results in COPD outpatients with comorbidities. Specifically, these authors found a significant improvement in 6MWD and SGRQ at the end of 8 weeks of physical training in all patients except for those with associated cardiovascular disease, even if stable. However, in contrast to the findings of the previous paper, the presence of cardiovascular comorbidities (n=16 patients, 26%) was not a significant predictor of poor response to pulmonary rehabilitation, although comorbidities did reduce the likelihood of reaching the MCID threshold for both 6MWD and SGRQ (OR 0.93 and 0.43, respectively).

More recently, an Italian group of researchers examined the potential effect of comorbidities on the rehabilitation outcome with a prospective trial at four Italian hospitals in 316 selected moderate and severe COPD outpatients [24]. There was no association between number and type of comorbidities (even if alone or in combination) and pulmonary rehabilitation effectiveness. Only the presence of osteoporosis was inversely related as a negative predictor in walking performance as assessed by 6MWD (OR 0.28, 95% CI 0.11–0.70). This was probably linked to specific factors such as bone frailty, muscle weakness and/or steroid-related myopathy, which typically occur in COPD patients.

This aspect of frailty related to osteoporosis and bone diseases has been confirmed in a study on >700 elderly patients admitted for physical rehabilitation after stroke and who had pre-existing Parkinson's disease or osteoarthritis [25]. In that study, which aimed at considering the independent role of comorbidities on the functional outcomes of balance and gait, the authors showed that the main determinants of poor physical recovery were characterised by a combination of disabling comorbidities, including osteoporosis and arthrosis, rather than the effect of each chronic disease, independent of age, cognitive status or functional status at admission.

With respect to the complexity of COPD, two other factors may also have a potential role on pulmonary rehabilitation efficacy. Indeed, chronic respiratory failure (CRF) and obesity may substantially compromise pulmonary function and the health status of COPD patients, thus, increasing the risk of death for all causes [26–29].

To examine the effectiveness of pulmonary rehabilitation in patients with CRF, an Italian observational, multicentre trial considered 327 severe and disabled COPD patients (forced expiratory volume in 1 s 37% predicted and baseline 6MWD of 283 m) [30]. After a standard programme, improvements in exercise tolerance and dyspnoea perception were similar when comparing those with CRF and those without (48 and 47 m in 6MWD and -0.85 and -0.73 points on the MRC score, respectively). A recent publication in COPD patients further confirmed these findings as there was no correlation between the presence of CRF and the success rate of rehabilitation [31].

Finally, the impact of obesity on rehabilitation outcomes in COPD patients has been evaluated in a retrospective study from a single centre [8]. The authors found that obesity did not adversely affect rehabilitation success: baseline exercise performance (6MWD) was similar between obese (BMI >30 $kg \cdot m^{-2}$) and nonobese COPD patients (203 *versus* 269 m walked) and both groups improved following pulmonary rehabilitation (47 and 52 m, respectively). A very recent prospective trial on 261 patients with severe COPD included being overweight as a potential factor of response to pulmonary rehabilitation. Although obese COPD patients had reduced walking capacity at baseline compared with nonobese patients, all participants, those of normal weight and those who were overweight and obese, improved walking capacity to a similar extent after pulmonary rehabilitation [32]. However, the percentage of subjects reaching the clinically significant change of 6MWD after rehabilitation was lower in obese (15%) compared with normal weight (24%) or overweight (18%) subjects. Interestingly, this was not the case for perceived quality of life. In a regression analysis, the changes in 6MWD distance and SGRQ scores were not statistically associated with the patients' body weight.

In conclusion, baseline characteristics appear too direct, in general, to identify the reasons for one person's success and another's failure in a pulmonary rehabilitation programme. Furthermore, there may be additional benefits to rehabilitation that are simply not detected by usual measures, for instance, improved social interaction, better sleep quality and greater confidence. Although there are some data suggesting that osteoporosis, metabolic syndrome and Charlson index may negatively impact on the outcome of pulmonary rehabilitation, the evidence is, at present, contradictory. Indeed, overweight patients and those with CRF appear to do as well as those without. As exercise is beneficial for most conditions, patients with COPD and comorbidities should be encouraged to take part in rehabilitation where able.

STATEMENT OF INTEREST

None declared.

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