Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease

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Summary

Background Respiratory rehabilitation is increasingly recognised as an important part of the management of patients with chronic obstructive pulmonary disease (COPD). The widespread application of such programmes should be preceded by evidence of directly attributable improvements in function. We assessed the effect of respiratory rehabilitation on exercise capacity and health-related quality of life (HRQL) in patients with COPD.

Methods We carried out a meta-analysis of randomised controlled trials of respiratory rehabilitation in patients with COPD that assessed functional or maximal exercise capacity, HRQL, or both. Respiratory rehabilitation was defined as exercise training (for at least 4 weeks) with or without education, psychological support, or both. The most commonly used measure for HRQL was the chronic respiratory questionnaire, in which responses were presented on a 7-point scale. The control groups received no rehabilitation. Within each trial and for each outcome an effect size was calculated; the effect sizes were then pooled by a random-effects model. The overall effect of treatment was compared with its minimum clinically important difference (MCID)—defined as the smallest difference perceived as important by the average patient.

Findings We included 14 trials. Significant improvements were found for all the outcomes. For two important features of HRQL, dyspnoea and mastery, the overall treatment effect was larger than the MCID: 1·0 (95% CI 0·6–1·5) and 0·8 (0·5–1·2), respectively, compared with an MCID of 0·5.

Interpretation Respiratory rehabilitation relieves dyspnoea and improves control over COPD. These improvements are clinically important. The value of the improvement in exercise capacity is not clear. Respiratory rehabilitation is an effective part of care in patients with COPD.

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Introduction Chronic obstructive pulmonary disease (COPD) is the fifth leading cause of mortality in north America and its prevalence continues to increase. The associated loss of physical capacity and the adverse psychological effects of the disorder contribute greatly to morbidity. Official organisations in north America and Europe endorse respiratory rehabilitation as integral to the long-term management of COPD, but reports of the benefits of this approach are mostly from uncontrolled trials and unsupervised therapy. Controlled trials have been limited by the lack of standard measurements of exercise tolerance and quality of life. Given the commitment asked of patients, their families, and health-care professionals, the interventions required must be justified by proof of improvement in exercise tolerance and quality of life. Moreover, if rehabilitation does benefit patients with COPD then it is important, before any widespread application, to know of the size of the treatment effect.

To establish the influence and effect size of respiratory rehabilitation on functional exercise capacity, maximum exercise capacity, and health-related quality of life (HRQL) in patients with COPD, we undertook a meta-analysis of all randomised controlled trials in which rehabilitation, including systemic exercise for at least 4 weeks, was offered to patients with COPD and in which treated patients were compared with control patients whose care in the community did not include rehabilitation.

Methods We searched Medline (1966 to October, 1995) and CINAHL (Cumulated Index to Nursing and Allied Health, 1982 to October, 1995) for original articles published in any language. For this search we used the following items: (exp, lung diseases, obstructive), (exp, rehabilitation or exp, exercise therapy), and (research design or longitudinal studies or evaluation study or randomised controlled trial). The reference lists of relevant articles were reviewed. In addition, abstracts presented at international meetings (American Thoracic Society, 1980–95, European Respiratory Society, 1987–94) were searched. We contacted investigators of studies included in the meta-analysis and experts in respiratory rehabilitation to locate any unpublished material.

We used the following criteria to select randomised controlled trials for inclusion in the meta-analysis.

Target population—We accepted trials in which more than 90% of patients had a clinical diagnosis of COPD and either a best recorded ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) of less than 0·7, or a best recorded FEV1 of less than 70% of the predicted value.

Respiratory rehabilitation programmes—We included any inpatient, outpatient, or home-based rehabilitation programme of at least 4 weeks duration that included exercise therapy with or without any form of education, psychological support for patients with exercise limitation attributable to COPD, or both.
Table 1: Characteristics of randomised trials included in meta-analysis

Primary outcome measures—were maximum or functional exercise capacity, HRQL, or both.

Methodological criteria—We required that randomised controlled trials compared respiratory rehabilitation with conventional community care or any other intervention unlikely to have any effect on exercise capacity or quality of life.

We looked at two potential sources of bias that have proved to be important determinants of the magnitude of the effect size in clinical trials: unconcealed randomisation and study investigators who were aware of treatment allocation. The former has been associated with an overestimation of the treatment effect by up to 40%; whereas the latter may result in differential encouragement associated with an overestimation of the treatment effect by up to 20%.

For multiple-group comparisons (eg, exercise therapy plus inspiratory muscle training compared with exercise therapy alone or with conventional community care), only the treatment group that received the more comprehensive therapy was included. This treatment group was compared with the group that received conventional community care.

Statistical analysis

The primary outcome measures, exercise capacity and HRQL, were treated as continuous outcomes. Several protocols have been recommended for exercise testing. Exercise capacity is commonly assessed by tests of maximum exercise capacity measured in terms of workload, energy, or oxygen consumption (eg, incremental cycle ergometry or treadmill tests), and tests of functional exercise capacity (eg, timed-walk tests). We decided to analyse maximum and functional test results separately because in this study we found only moderate correlations (r=0·52–0·81) between maximum exercise capacity and functional exercise capacity.

Only instruments for which there was evidence of validity (the ability of an instrument to measure what it claims to measure)
and responsiveness (the ability to detect real change, even when it is small) were included in the meta-analysis of HRQL.

In each trial and for every outcome measure, we calculated the treatment effect from the difference between the preintervention and postintervention changes in the treatment and control groups. Most related outcome measures were expressed across studies within different units; we, therefore, standardised the resulting treatment effects to obtain an effect size by division of treatment effects by the pooled SD value of the postintervention outcome measure in the treatment and control groups. The effect sizes were weighted by the inverse of the population variance and combined according to a random-effects model. This model assumes that: the studies included in the meta-analysis are a random sample from a larger population of studies (to include uncovered, uncompleted, or planned trials); and that the estimate of effect size in each study differs from the population effect size because of sampling error. Homogeneity among study results was tested. The pooled effect sizes and corresponding 95% CIs were reported for each outcome in SD units, and then converted back to natural units of the most commonly used measure. Whenever possible, the overall treatment effect expressed in natural units was compared with its minimum clinically important difference (MCID)—defined as the smallest difference perceivable by the average patient. When the magnitude of the treatment effect equals or exceeds the MCID, the management of a patient should be changed, unless there are adverse side-effects or excessive costs.

Subgroup analyses were indicated when significant heterogeneity was found among the primary findings of the trials, or when no heterogeneity was found among trial results but when the clinical significance of the overall treatment effect was borderline—ie, when the CI for the overall effect encompassed the MCID.

To explain anticipated heterogeneity among trial findings, three respiratory disease physicians (YL, EW, RSG) identified, a priori, potential sources of heterogeneity among the outcomes of exercise capacity and HRQL. Since the treatment effect might vary according to the severity of disease, population was judged a likely source of heterogeneity. In addition, we postulated that: the more comprehensive the rehabilitation programme, the larger the effect size in improving exercise capacity and HRQL; that patients in short-duration rehabilitation programmes (<8 weeks) would achieve greater improvements than those in unsupervised, home-based programmes. We also postulated that the findings of trials would be affected by the quality of the methods used—particularly in terms of double-blind conditions for the assessment of the primary outcome measures.

Results

301 publications were retrieved from the computer searches and 54 abstracts were identified. Three studies were found through our contact with experts. The publications were reduced to 81 potentially eligible papers. 64 trials were excluded because: the population of patients assessed was inappropriate (two studies); the intervention did not meet the definition of rehabilitation (11); the control groups did not receive conventional community care (27); or trials were not randomised (24). Both reviewers (YL, EW) agreed to include 15 papers in the meta-analysis (quadratic weighted k=0.79 [95% CI 0.58–1.00]). The reviewers disagreed about two papers, but both were included after consultation with the third reviewer (RG). Of the 17 reports of the 16 trials judged acceptable, two were excluded because they did not have adequate data, even after contact with the investigators. T able 1 shows the 14 trials that were included in the meta-analysis. We contacted the authors of these papers for any additional information required; the response rate was 100%.

Of the 14 trials, one did not meet our criteria for randomisation. Consequently, we defined subgroups only on the basis of whether the outcome assessment was masked.

Table 2 shows important demographic and clinical characteristics of the patients at study entry in each trial. Most patients were elderly and had severe COPD. The main exclusion criteria were: ischaemic heart disease, heart failure, intermittent claudication, disabling musculoskeletal disorders, domiciliary oxygen requirement, hypercapnia, and other medical disorders that limited exercise tolerance.

Maximum exercise capacity was measured in 11 trials (309 patients). The pooled effect size achieved significance (0.3 SD units [95% CI 0.1–0.6]) and corresponded to incremental cycle ergometer test natural units, to 8.3 W (2.8–16.5). Homogeneity was found among study findings (p=0.85), which suggests that the effect of rehabilitation on maximum exercise capacity was constant across studies, irrespective of the duration or composition of the rehabilitation programme.

The effect of respiratory rehabilitation on functional exercise capacity are shown in the figure. 11 trials (413 patients) were included in this analysis. After conversion back to natural units for the 6-min walk test (m), a difference in response between the treatment and control groups of 55–7 m (28.6–92.8) was found. We estimated the MCID of the walk test at about 50 m from a study in which COPD patients rated their walking ability by subjective comparisons with one another. The limits of the CI for the pooled estimate of effect size (27.8–92.8) were wider than those of the estimate of the MCID of the 6-min walk test (37–71 m). Heterogeneity among study results (p=0.0008) could not be explained by the subgroup analyses. A post-hoc analysis based on the observed results showed a significant difference between the programmes of 6 months duration and the other

<table>
<thead>
<tr>
<th>Study</th>
<th>Favours control</th>
<th>Favours treatment</th>
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<tr>
<td>McGavin, 1977</td>
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<td>Cockcroft, 1981</td>
<td></td>
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<td>Booker, 1984</td>
<td></td>
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<tr>
<td>Jones, 1985</td>
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<td>Lake, 1990</td>
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<td>Simpson, 1992</td>
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<td>Weiner, 1992</td>
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<td>Goldstein, 1994</td>
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<td>Wijkstra, 1994</td>
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<tr>
<td>Güell, 1995</td>
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<td>Strijbos, 1996</td>
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Overall effect: 0.6 (0.3 to 1.0)

Figure: Effect of respiratory rehabilitation on functional exercise capacity
programmes (93.8 m [homogeneity, p=0.31] vs 39.2 m [homogeneity, p=0.10]; difference, p=0.0004). Since this analysis was data-driven the results should be interpreted as hypothesis-generating.

12 of the 14 trials measured HRQL and ten different instruments were used for this assessment (table 1). Evidence of validity and responsiveness for only two of these instruments has been published (the transitional dyspnoea index,\textsuperscript{30} and the chronic respiratory questionnaire\textsuperscript{31}). We, therefore, confined the analysis of HRQL to the six trials in which one of these questionnaires had been used. The most frequently used measure was the chronic respiratory questionnaire, in which responses were presented on a 7-point scale. For each outcome, the overall effect size exceeded the M CID (0.5 points). CI values suggest that the smallest treatment effect exceeded the M CID for the dimensions of dyspnoea and mastery (the extent to which patients feel they can cope with the disease and its manifestations); whereas for fatigue and emotional function the CI values encompassed the M CID.

We analysed fatigue and emotional function for sources of heterogeneity, but the small number of trials limited the power of the subgroup analyses. No a-priori hypotheses accounted for differences in individual trial results.

Discussion

The development of objective HRQL outcome measures and better understanding of the physiological rationale for exercise training in patients with COPD\textsuperscript{25} have facilitated the widespread acceptance of respiratory rehabilitation.

We would like to comment on three features of our meta-analysis. First, we assessed the acute effect of respiratory rehabilitation on COPD—ie, the benefits of rehabilitation at the completion of a programme. Further studies are needed to assess the long-term benefits of rehabilitation and strategies to maintain the early benefits. Second, the criterion we used to define a clear benefit of respiratory rehabilitation was conservative: the lower limit of the CI had to be greater than the M CID. Third, several well-conducted studies were excluded from the meta-analysis because we focused on the effect of rehabilitation when added to conventional care. We, therefore, excluded one well-conducted trial, because the control group received an educational intervention.\textsuperscript{33} Similarly, we excluded studies that compared interventions, such as inspiratory muscle training, psychosocial support, or breathing exercises, with exercise training.

The care of patients with COPD largely aims to address symptoms and, therefore, we believe that quality of life and functional exercise capacity should be the primary outcome measures for respiratory rehabilitation. Our meta-analysis shows that respiratory rehabilitation relieved dyspnoea and improved mastery, because the magnitude of the improvement was greater than the M CID. By contrast, the clinical importance of functional exercise capacity is not clear because the CI of the effect size was wider than that of the M CID for the 6-min walk test. Although rehabilitation programmes included in the meta-analysis differed in several ways, for example, in clinical settings, duration, and composition, the homogeneity among study results suggests that less sophisticated rehabilitation programmes may be as effective as the more comprehensive programmes in improving HRQL.

The importance of measures of maximum exercise capacity is not clear. We believe that an initial test may be useful to establish the appropriate level of training. Re-testing may provide physiological evidence that a training response has occurred and may, therefore, be used to adjust intensity levels during rehabilitation.\textsuperscript{4} Since the results of maximum exercise tests correlate poorly with HRQL measures,\textsuperscript{7} such tests should not be substituted for measures of HRQL in the assessment of a rehabilitation programme.

Our findings strongly support respiratory rehabilitation that includes at least 4 weeks’ exercise training as part of management for patients with COPD. We found clinically and statistically significant improvements in dyspnoea and mastery. When compared with the treatment effect of other important approaches for patients with COPD, such as bronchodilators or oral theophylline,\textsuperscript{49,50} rehabilitation led to greater improvements in HRQL and functional exercise capacity.

Table 3: Primary results of meta-analysis

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Number of trials (treatment/control)</th>
<th>Total number of patients</th>
<th>Effect size (SD units)</th>
<th>Treatment effect (natural units)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum exercise capacity</td>
<td>11/160/149</td>
<td>0.3 (0.1–0.6)</td>
<td>0.3 W</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Functional exercise capacity</td>
<td>11/211/202</td>
<td>0.6 (0–3–1)</td>
<td>55.7 m</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4/111/96</td>
<td>0.8 (0.5–1.2)</td>
<td>1.0 (0–6–1.5)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4/111/96</td>
<td>0.6 (0.3–0.8)</td>
<td>0.8 (0–4–1.9)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>4/111/96</td>
<td>0.5 (0–2–0.8)</td>
<td>0.6 (0–2–1.2)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>4/111/96</td>
<td>0.6 (0–4–0.9)</td>
<td>0.8 (0–5–1.2)</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

*Natural units are from individual items (7-point scale) of the chronic respiratory questionnaire (dyspnoea, fatigue, emotional function, mastery), an incremental cycle ergometer test (maximum exercise capacity), and a 6-min walk test (functional exercise capacity).

We thank the authors of the primary studies included in the meta-analysis who provided additional data and information about their work.

References
