

COPD patients' ability to follow exercise influences short-term outcomes of rehabilitation

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Abstract

COPD patients with limited ability to follow exercise protocols may have smaller benefits from rehabilitation. We assessed the association between the ability to follow exercise protocols and short-term outcomes of rehabilitation in COPD patients.

As measure of the ability to follow exercise protocols, we determined the number of major breaks of ≥ 1 minute of 98 COPD patients during supervised exercise sessions. We compared benefits from rehabilitation between patients with, on average, >1 and ≤ 1 major breaks per session.

Patients with ≤ 1 major break per session showed significantly greater improvements of exercise capacity (between-groups difference of 38 meters [95% CI 8-68] for Six-minute walk distance, 22.1 Watt [5.5-38.7] for short-time maximum exercise capacity [steep ramp test] and 5.5 Watt [0.1-11.1] for maximum exercise capacity). Quality of life also tended to be better in patients with ≤ 1 major break per session, but differences were not significant (adjusted between-groups difference of 0.14 [-0.37-0.66]).

Limited ability to follow exercise protocols is associated with smaller benefits from rehabilitation. This finding highlights the importance of choosing tolerable exercise protocols for COPD patients.

Key words:

COPD

Exercise

Exercise Test

Quality of Life

Respiratory Rehabilitation

Background

Physical exercise plays a critical role in the Chronic Obstructive Pulmonary Disease (COPD) management.[1-3] It improves health-related quality of life (HRQL) and is likely to lower the risk for hospital admissions and death.[4, 5] However, patients with advanced COPD are often limited by dyspnea and fatigue rendering physical exercise difficult. Great research efforts were made in the last decade to find tolerable but at the same time effective exercise protocols.[6]

Continuous and interval exercise have become the most widely applied protocols for lower limb training in COPD patients.[4, 6] During continuous exercise, patients exercise at a constantly high work workload of around 70% of maximum exercise capacity. During interval exercise, patients exercise alternatively at high and low workload to allow patients to recover intermittently from the high workload intervals. It is thought that a lower degree of dynamic hyperinflation results from interval exercise compared to continuous exercise, which is associated with good tolerance of this exercise modality.[7-9] We and other investigators showed in randomised trials that interval exercise is not less effective than continuous exercise to improve HRQL and exercise capacity of patients with COPD.[10-14]

Little attention has been paid to the ability of patients to follow specific exercise protocols and whether this has consequences on short-term outcomes of respiratory rehabilitation. If an exercise protocol is tolerated well during the supervised initiation stage of exercise it may motivate patients to continue their training and increase attendance of exercise sessions. These questions have not been addressed empirically. Therefore, the aim of this study was to assess the ability of patients with severe COPD to follow continuous and interval exercise protocols and to explore the consequences on short-term benefits.

Methods

Design Overview

We recently described the methods and main results of this randomised, controlled non-inferiority trial.[13] In brief, we compared the effects of interval exercise and high intensity continuous exercise in 98 patients with COPD stage III-IV according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). We excluded patients with cardiovascular, musculoskeletal or neurological co-morbidities only if they were likely to inhibit physical exercise or the performance of exercise tests. Patients were randomly assigned to either high-intensity continuous exercise or interval exercise using a computerised minimisation procedure, thereby ensuring balanced and concealed randomization. The trial took place in a public rehabilitation clinic in Switzerland (Klinik Barmelweid, Aargau). The responsible ethics committee approved the study protocol and all study participants provided written informed consent.

Interventions

Patients followed an inpatient respiratory rehabilitation of approximately 3 weeks duration that included 12 to 15 exercise sessions of 25 minutes duration that was followed by individually prescribed home-based exercise (the median number of total sessions during the inpatient program was 13 and 22 following including the 2 weeks of home-based exercise, respectively[13]). Patients randomised to continuous exercise trained on electromagnetically braked cycle ergometers with a target workload of 70% of maximum exercise capacity. The target workload for interval exercise was 50% (high-intensity intervals) and 10% (low-intensity intervals) of the patients' short-term maximum exercise capacity as determined by a steep ramp test. We have described this test in detail.[13] The work-recovery ratio was 1:2 with high-intensity intervals of 20 seconds and low intensity intervals of 40 seconds. Apart from exercise, the rehabilitation program

was identical for both groups and included patient education, breathing therapies and optimisation of medical therapy.

Outcomes

The number of unintended breaks of ≥ 1 minute due to dyspnea, leg pain or other complaints was our primary outcome for the ability to follow assigned exercise protocols during supervised exercise sessions. We considered this to be an adequate measure for the ability to follow exercise protocols because a break represents a well-defined and measurable consequence of excessive strenuous exercise. The breaks were recorded by physiotherapists on the clinics' routine exercise diary. Patients were not aware that breaks were recorded. We did not compare symptom ratings or heart rate between groups as a measure of the ability to follow exercise protocols. If these parameters are used to guide adjustment of exercise intensity, as in our study, they become ineligible as outcome measures because interventions and outcomes must be independent from each other.

As measures for the effects of respiratory rehabilitation, we used the German self-administered, standardised Chronic Respiratory Questionnaire (CRQ)[15, 16], Six-minute walk distance as well as short-time maximum exercise capacity (steep ramp test) and maximum exercise capacity (incremental exercise test). We have described the measurements of these outcomes in detail.[13]

Statistical Analysis

Consequences of different levels of ability to follow exercise protocols on short-term outcomes of respiratory rehabilitation

To enhance comparability across patients, we calculated the number of breaks per exercise session since the number of exercise sessions varied slightly across patients (median number of sessions 13 [interquartile range 12-14], 91 patients (93%) followed ≥ 11 sessions[13]). We categorised patients into two groups with, on average, ≤ 1 or > 1 break per exercise session. We compared the changes in exercise capacity and HRQL between these two groups using linear regression analyses without and with adjustment for disease severity (dyspnea, hyperinflation, hypoxemia, baseline exercise capacity) and other characteristics (age, gender, group allocation) that might influence the association between the ability to follow exercise protocols and short-term outcomes of rehabilitation. We did not adjust for dyspnea for HRQL because the dyspnea measure is part of the CRQ (dependent variable).

Subgroup analysis

Before conducting the current analyses, we determined the predictor variables based on previous studies and plausible associations of the ability to follow exercise protocols and the outcomes of rehabilitation.[7-9, 17] We did, however, not design or power our trial for subgroup analyses in its planning stage.[17][18, 19] The nature of these a posteriori subgroup analyses are, therefore, of explorative nature. We restricted subgroup analyses to the following six predictors: Dyspnea as measured by the CRQ dyspnea domain, hypoxemia (resting partial oxygen pressure in arterial blood), static hyperinflation as reflected by the resting intrathoracic gas volume (expressed as % predicted), Six-minute walk distance, recent exacerbations (\leq or > 8 weeks) and depressive symptoms (\leq or > 8 points on Hospital Anxiety and Depression Scale). We had used four of these variables (hypoxemia, Six-minute walk distance, recent exacerbation and depressive symptoms) as stratification variables in the randomisation process as described to achieve balanced groups. This indicates our a priori predictions

regarding their relation to the ability to follow exercise protocols.[17] We did not include standard parameters for COPD severity such as FEV₁ or combined indices as predictor variable as there is no evidence from earlier studies that it does influence the association between the ability to follow exercise protocols and the outcomes of rehabilitation.

For each of the predictor variables, we divided patients within the interval and continuous exercise group into tertiles reflecting moderate, severe and very severe impairment. Thus patients with lowest scores between the 1st to 33rd percentile (=1st tertile) were defined to have very severe impairment, patients with scores between the 34th to 66th percentile to have severe impairment and patients with scores between the 67th to 100th percentile to have moderate impairment. For each of these groups we calculated means and standard deviations (SD) for the predictor variables (table 1). As recommended for formal subgroup analyses we evaluated the presence of subgroup effects testing for interaction[19, 20] and by looking graphically at the trend across subgroups. We used a $p < 0.05$ as a very conservative cut-off for statistically significant and clinically relevant interaction. We conducted linear regression analyses with our primary outcome, the number of unintended breaks, as the dependent and group, the predictor variable and the interaction term as independent variables. We also transformed the number of breaks per session by taking the square root. With this transformation, residuals of the linear regression analyses were distributed normally. We back-transformed the results from the linear regression analyses to present the data and to facilitate interpretation. We performed all analyses using SPSS 12.0.1 for Windows (SPSS Inc, Chicago, Ill).

Results

We included all 98 patients (66.3% male) enrolled in the trial in this analysis. Mean age was 68.9 years (SD 9.1), FEV₁ 34.3% predicted (8.5), CRQ dyspnea at baseline 2.94 (0.97), baseline Six-minute walk distance 323 meters (109), body mass index 24.7 kg/m² (6.4) and 58.2% had cardiovascular co-morbidities.

Consequences of different levels of ability to follow exercise protocols on outcomes of respiratory rehabilitation

Figure 1 shows that patients with >1 unexpected break per exercise session showed consistently lower effects of rehabilitation than patients with ≤ 1 unexpected break per exercise session. For example, patients with >1 break per exercise session showed a mean improvement of only 22 meters (SD 69) in Six-minute walk distance whereas patients with ≤ 1 break per exercise session had a mean improvement of 53 (SD 52) meters.

Figure 2 shows unadjusted and adjusted differences in outcomes between patients with >1 or ≤ 1 break per exercise session. In multivariable regression models ≤ 1 break per exercise session was independently associated with a substantially larger improvement of Six-minute walk distance (38 meters, 95% CI 8-68, P=0.01). We also observed larger improvements for short-time (p=0.01) and normal maximum exercise capacity (p=0.05) in patients with ≤ 1 break per exercise session. Unadjusted analyses also suggested a larger effect on HRQL (p=0.05), but adjustment for disease severity reduced the difference between the two groups (p=0.62).

Subgroup analysis

Table 1 shows the characteristics of the subgroups. In general, patients in the corresponding subgroups of the interval and continuous exercise groups showed similar

degrees of impairment. For example, patients with the least degree of hyperinflation (moderate) in the interval and continuous exercise group had mean intrathoracic gas volume of 126% predicted (SD 20) and 130% predicted (SD 17) at study entry, respectively, whereas the 33% of patients with most severe hyperinflation had mean intrathoracic gas volumes of 207% predicted (SD 26) and 206% predicted (SD 22), respectively. Patients with moderate and severe dyspnea had somewhat lower mean dyspnea scores than corresponding subgroups in the continuous exercise group. Patients with most severe dyspnea, however, had similar dyspnea scores. In the interval exercise group 29 patients (60.4%) experienced a recent exacerbation compared to 30 patients (60.0%) in the continuous exercise group.

Figure 3 shows the subgroup analyses. Patients with moderate dyspnea tolerated interval and continuous exercise similarly (difference in number of unexpected breaks per exercise session of 0.1, 95% CI -0.3 to 0.5). Patients with more severe dyspnea at study entry required more breaks in the continuous exercise group compared to patients in the interval exercise group (difference 0.4, 95% CI -0.2-1.1 for patients with severe and 0.8, 95% CI 0.0-1.6 for patients with very severe dyspnea). Testing for the subgroup effect (interaction for group*dyspnea) showed a p-value of $p=0.08$.

We observed similar results for the subgroup analyses of hypoxemia, hyperinflation and Six-minute walk distance. Again, the more severe impairment the greater the difference in the number of breaks became: This trend was more pronounced and significant for hypoxemia ($p=0.04$ for subgroup effect) than for hyperinflation ($p=0.15$ for subgroup effect) and Six-minute walk distance ($p=0.17$ for subgroup effect). The two remaining subgroup variables, recent exacerbation and depressive symptoms, were not related to the number of breaks ($p=0.49$ for subgroup effect and $p=0.59$, respectively).

Discussion

This study shows that the ability to follow exercise protocols plays an important role as predictor of enhanced short-term benefits from respiratory rehabilitation. Patients with ≤ 1 major breaks per exercise session had significantly larger improvements of exercise capacity than patients with >1 break. Improvements in HRQL were significantly larger in unadjusted analyses only. Our study also suggests that the degree of impairment as expressed by the degree of dyspnea, exercise capacity, hyperinflation and hypoxemia may influence how well patients can follow interval exercise compared to continuous exercise. However, this subgroup analysis was not pre-planned and only some of the differences were statistically significant.

A strength of our analysis is that the data come from a randomised trial with high quality methods. Another strength is the implementation of the trial in an everyday clinical setting with typical COPD patients. In addition, we determined predictor variables that were biologically or clinically plausible before performing any subgroup analyses and that we had in part already identified as possible effect modifiers during the planning phase of the trial. In addition, we followed recommended standards for the exploration of subgroup effects using interaction terms in regression analyses.[19]

A major limitation is that our trial was, a crux for most subgroup analyses, not powered sufficiently for the subgroup analyses. We based the sample size calculation only on the main comparison of the trial.[13] In addition, a limitation of restricting subgroup analyses to six variables is that more plausible predictor variables may exist. However, restricting the number of predictor variables (6) decreased the risk of finding subgroup effects due to chance.[18] Finally, we recorded medical emergencies and accidents during exercise sessions only (we did not observe any) but we did not register the reasons for each major break.

To our knowledge, this is the only COPD trial that assesses the consequences of the ability to follow specific exercise protocols on short-term outcomes. The focus on this aspect is important for several reasons. As our analysis showed, patients have more short-term benefit from rehabilitation if they can follow the exercise protocol without major breaks. Differences in improvements of exercise capacity were substantial and not affected much by adjustment. In contrast, HRQL was different between groups in unadjusted analyses only. Adjustment for baseline hyperinflation and other parameters moderated between-group differences, which indicates their effect on improvements of HRQL.

Experiencing a tolerable exercise protocol during the supervised initiation phase of exercise may also be important in the long-term. Many COPD patients exercise for the first time after a period of physical inactivity. To facilitate this initiation it is important that patients tolerate the exercise well and perceive short-term benefit as it will likely improve adherence to training programs in the long-term. We have not addressed this aspect but future studies may inform us in this regard. Also, our parameter for the ability to follow exercise protocols, the average number of major breaks, was rather simple. This simple parameter makes it attractive for trials and practice but it does not offer a more differentiated analysis of exercise tolerance. Future trials on exercise in COPD should evaluate whether better measures for the ability to follow exercise can be developed. Thereby, one would learn more about this important aspect for clinical practice.

Previous studies suggested that interval exercise is particularly well tolerated by patients with severe COPD.[7-9] The low intensity intervals limit dynamic hyperinflation, which is most pronounced in severely impaired COPD patients. Based on these studies, we selected parameters for impairment that are readily available in clinical practice. As noted above, our study was too small to show statistically significant subgroup effects

and it is possible that the results are due to chance. However, there is no prior evidence answering this question from respiratory rehabilitation trials. We found a trend that the most severely impaired patients who enter rehabilitation tolerate interval exercise better than continuous exercise, but to confirm these findings additional larger studies are needed. Investigators commonly use more lenient thresholds such as $p < 0.1$ or $p < 0.2$ for interaction effects. We considered subgroup effects to be significant if p-values for interaction terms were ≤ 0.05 . We decided to use this conservative threshold because of the number of predictor variables. If we had used a higher threshold for significance, dyspnea would have been a significant predictor, too.

It would be important that future trials plan subgroup analyses in advance and power their trials accordingly. Thereby, one would learn more about variables available in clinical practice that guide the selection of exercise protocols. For clinicians, it would be attractive to use these parameters in combination. For example, one could develop a simple score containing parameters such as dyspnea, hyperinflation, hypoxemia or exercise capacity to predict tolerance of specific exercise protocols.

Conclusion

Our study showed that it is important to select an exercise protocol that COPD patients are able to follow. If patients need at least one major break of ≥ 1 minute per exercise session, they are less likely to benefit from respiratory rehabilitation, at least in the short term. Interval and continuous exercise are prudent choices for COPD patients with GOLD stage III to IV if they show moderate impairment due to increased dyspnea, hypoxemia, hyperinflation or moderately reduced exercise capacity. If patients are severely impaired, interval exercise is likely to be better tolerated than continuous exercise.

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References

1. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society 1999, 159(4 Pt 2):S1-40.
2. Global initiative for chronic obstructive pulmonary disease - gold workshop report. 2006. Available from: <http://www.goldcopd.com/> last access February 20, 2007
3. Managing stable COPD. *Thorax* 2004, 59(90001):39i-130.
4. Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, Goldstein RS: Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2004(4):CD003793.
5. Puhan MA, Scharplatz M, Troosters T, Steurer J: Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality -- a systematic review. *Respir Res* 2005, 6:54.
6. Puhan MA, Schunemann HJ, Frey M, Scharplatz M, Bachmann LM: How should COPD patients exercise during respiratory rehabilitation? Comparison of exercise modalities and intensities to treat skeletal muscle dysfunction. *Thorax* 2005, 60(5):367-375.
7. Sabapathy S, Kingsley RA, Schneider DA, Adams L, Morris NR: Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. *Thorax* 2004, 59(12):1026-1031.
8. Vogiatzis I, Georgiadou O, Golemati S, Aliverti A, Kosmas E, Kastanakis E, Geladas N, Koutsoukou A, Nanas S, Zakynthinos S et al: Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. *Thorax* 2005, 60(9):723-729.
9. Vogiatzis I, Nanas S, Kastanakis E, Georgiadou O, Papazahou O, Roussos C: Dynamic hyperinflation and tolerance to interval exercise in patients with advanced COPD. *Eur Respir J* 2004, 24(3):385-390.
10. Arnardottir RH, Sorensen S, Ringqvist I, Larsson K: Two different training programmes for patients with COPD: a randomised study with 1-year follow-up. *Respir Med* 2006, 100(1):130-139.
11. Coppoolse R, Schols AM, Baarends EM, Mostert R, Akkermans MA, Janssen PP, Wouters EF: Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J* 1999, 14(2):258-263.
12. Kaelin MB, K;Swank,A;Adams,K.;Ponto, A. Results of 6 minute ambulation and met tolerance of patients with severe chronic obstructive pulmonary disease (copd) utilizing 2 different aerobic training regimes: Interval training versus continuous training. *American Society of Exercise Physiology*., 2nd Annual Meeting 1997.
13. Puhan MA, Busching G, Schunemann HJ, VanOort E, Zaugg C, Frey M: Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease: a randomized trial. *Annals of internal medicine* 2006, 145(11):816-825.
14. Vogiatzis I, Nanas S, Roussos C: Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J* 2002, 20(1):12-19.
15. Puhan MA, Behnke M, Frey M, Grueter T, Brandli O, Lichtenschopf A, Guyatt GH, Schunemann HJ: Self-administration and interviewer-administration of the German Chronic Respiratory Questionnaire: instrument development and assessment of validity and reliability in two randomised studies. *Health Qual Life Outcomes* 2004, 2(1):1.
16. Puhan MA, Behnke M, Laschke M, Lichtenschopf A, Brandli O, Guyatt GH, Schunemann HJ: Self-administration and standardisation of the chronic

respiratory questionnaire: a randomised trial in three German-speaking countries. *Respir Med* 2004, 98(4):342-350.

17. Puhan MA, Busching G, VanOort E, Zaugg C, Schunemann HJ, Frey M: Interval exercise versus continuous exercise in patients with moderate to severe chronic obstructive pulmonary disease--study protocol for a randomised controlled trial [ISRCTN11611768]. *BMC Pulmonary Medicine* 2004, 4:5.
18. Oxman AD, Guyatt GH: A consumer's guide to subgroup analyses. *Annals of internal medicine* 1992, 116(1):78-84.
19. Rothwell PM: Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 2005, 365(9454):176-186.
20. Pocock SJ, Assmann SE, Enos LE, Kasten LE: Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Statistics in medicine* 2002, 21(19):2917-2930.

Legends for figures

Figure 1: The figure shows mean changes (\pm SD) in outcomes of rehabilitation for patients with good adherence to exercise (≤ 1 unexpected break per exercise session) and poor adherence (> 1 breaks per exercise session).

Figure 1

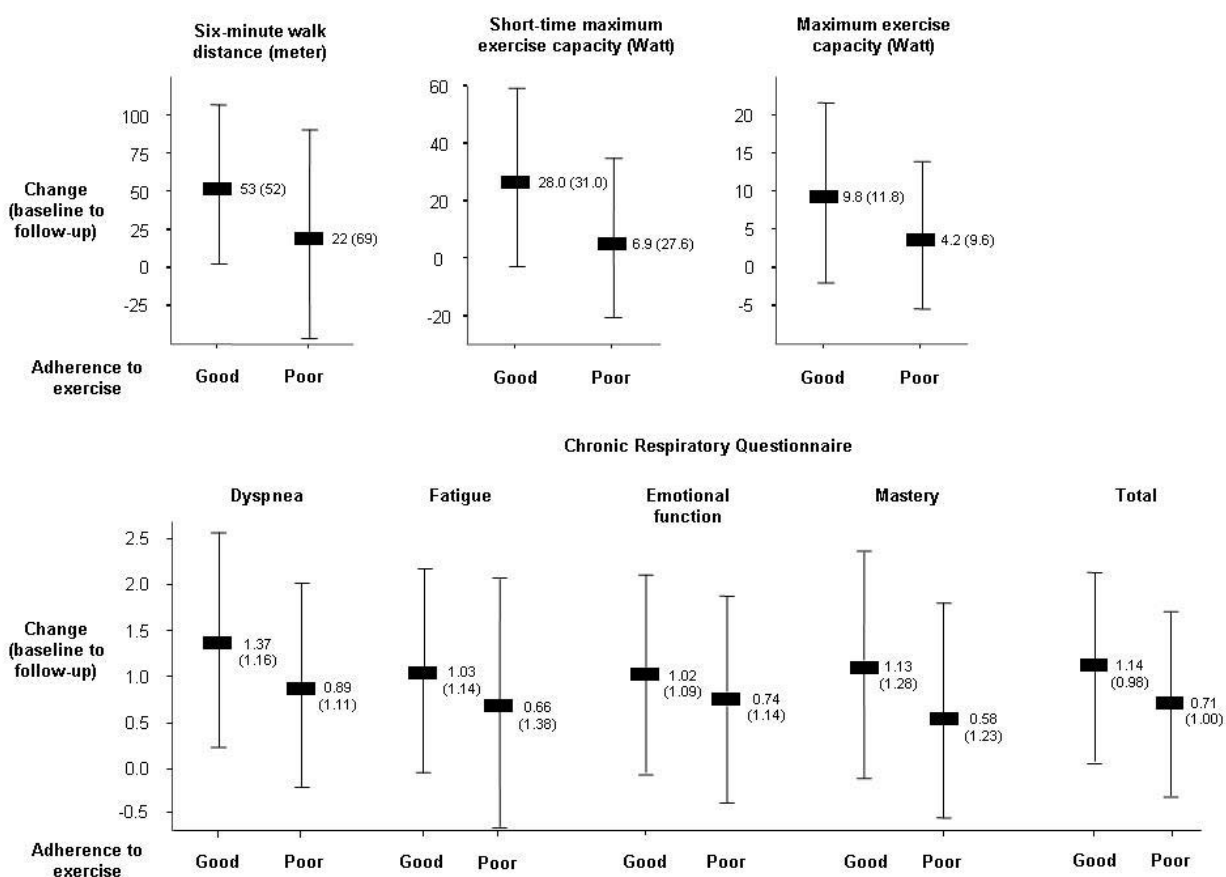
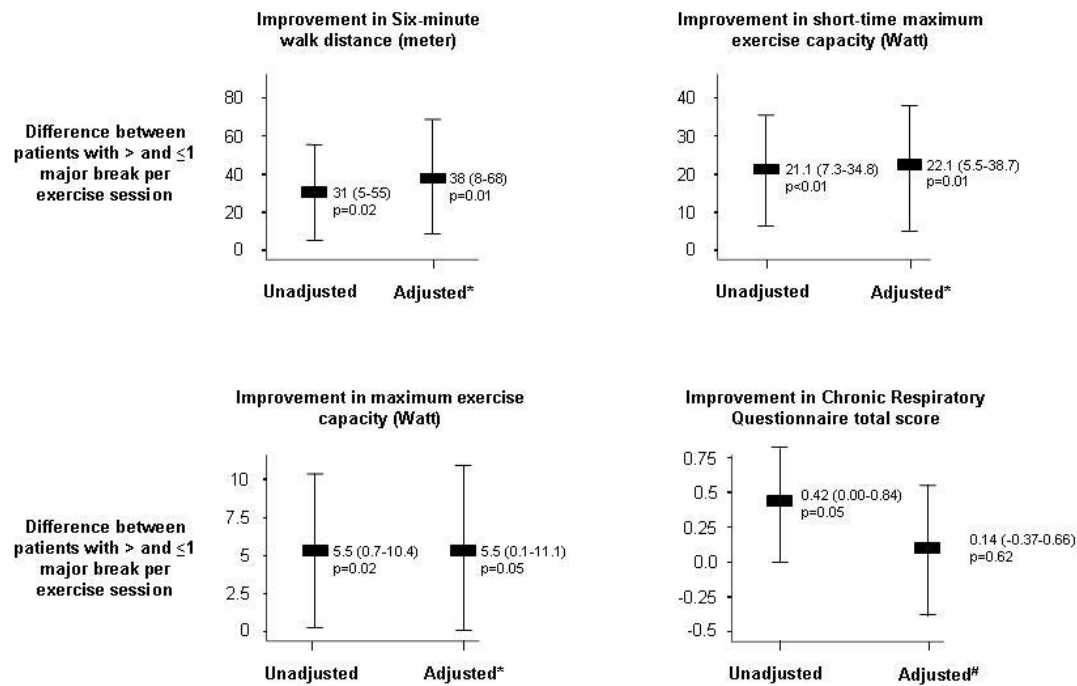


Figure 2: The figure shows unadjusted and adjusted mean differences (95% CI) in improvement of outcomes between patients with good adherence to exercise (≤ 1 unexpected break per exercise session) and poor adherence (> 1 breaks per exercise session).

Figure 2



* Adjusted for age, gender, group, Six-minute walk distance, dyspnea, hypoxemia and hyperinflation

Adjusted for age, gender, group, Six-minute walk distance, hypoxemia and hyperinflation

Figure 3: The figure shows the six subgroup analyses. For each predictor variable (for example dyspnea) and subgroup (for example moderate), the difference between the interval and continuous exercise subgroups in breaks per exercise session is shown together with the 95% confidence interval. Positive differences mean more breaks with continuous exercise. The p-values for subgroup effects stem from the interaction term (predictor variable*subgroup) in the multivariable regression analyses.

Figure 3

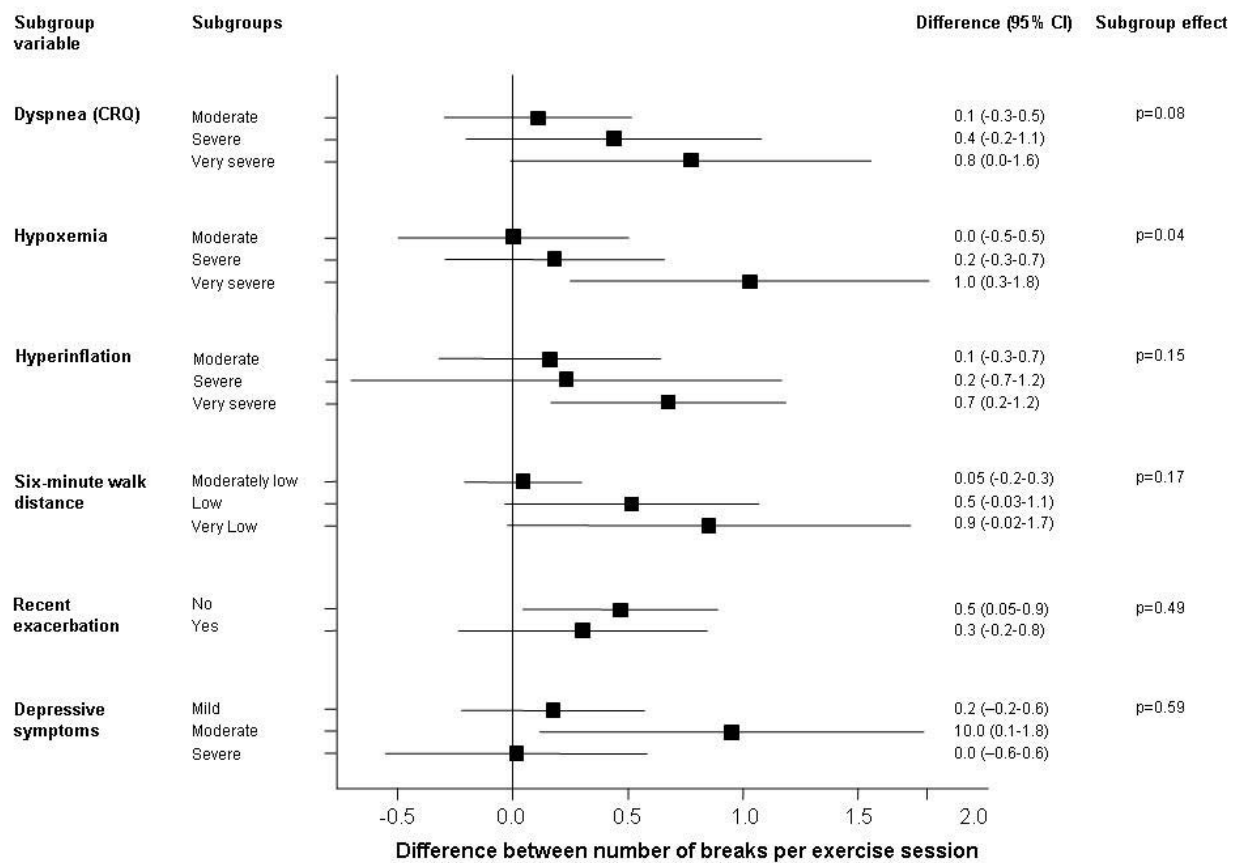


Table 1: Characteristics of the subgroups

Subgroup variable	Interval exercise group (n=48)			Continuous exercise group (n=50)		
	Moderate	Severe	Very severe	Moderate	Severe	Very severe
Dyspnea (Chronic Respiratory Questionnaire)	3.78 (0.50) n=17	2.79 (0.18) n=15	1.86 (0.47) n=16	4.18 (0.44) n=17	3.03 (0.36) n=16	1.89 (0.48) n=17
Hyperinflation (intrathoracic gas volume in % predicted)	126 (20) n=13	162 (8) n=13	207 (26) n=15	130 (17) n=15	158 (8) n=16	206 (22) n=15
Arterial oxygen pressure in mm Hg	67.0 (3.5) n=15	58.1 (2.2) n=15	48.1 (5.5) n=18	70.4 (3.6) n=16	60.4 (2.6) n=15	49.5 (5.2) n=19
Six-minute walking distance in meters	434 (56) n=16	309 (24) n=16	196 (50) n=16	458 (57) n=17	321 (27) n=17	211 (44) n=16
Depression (Hospital Anxiety and Depression Scale)	3.89 (1.45) n=18	7.33 (0.62) n=15	12.67 (2.53) n=15	3.41 (1.37) n=17	7.63 (1.12) n=19	12.46 (2.50) n=14

Values are means (standard deviation)

For 7 patients with interval exercise and 4 patients with continuous exercise no data about hyperinflation were available.