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Interval versus Continuous High-Intensity Exercise in Chronic Obstructive Pulmonary Disease

A Randomized Trial

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Background: Guidelines recommend high-intensity continuous exercise to reduce peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease but acknowledge that interval exercise might be an equally effective alternative that is better tolerated by patients.

Objective: To assess whether interval exercise is no less effective than high-intensity continuous exercise and whether it is tolerated better by patients with severe chronic obstructive pulmonary disease.

Design: Randomized, noninferiority trial.

Setting: Publicly funded rehabilitation hospital in Switzerland.

Patients: 98 patients with severe chronic obstructive pulmonary disease, with or without recent exacerbations.

Intervention: 12 to 15 supervised interval or high-intensity continuous exercise sessions (over 3 weeks) followed by exercise at home.

Measurements: Health-related quality of life determined by using the Chronic Respiratory Questionnaire (CRQ) (scores from 1 [most severe impairment] to 7 [no impairment]) after 5 weeks and number of unintended breaks during supervised exercise.

Results: Both groups experienced large improvements in health-related quality of life (increase of CRQ total scores of 1.00 [SD, 0.98] for the interval exercise group and 1.02 [SD, 1.05] for the continuous exercise group). Adjusted between-group differences between the interval exercise group and the continuous exercise group (−0.05 [95% CI, −0.42 to −0.32] for CRQ and 1.1 meters [CI, −25.4 to 27.6 meters] for 6-minute walking distance) were within the a priori defined boundaries of noninferiority (0.5 for CRQ and 45 meters for 6-minute walking distance). Twenty-one (47.9%) patients using interval exercise and 11 (24.0%) patients using continuous exercise were able to adhere to the protocol (difference, 23.9 percentage points [CI, 5.0 to 42.8 percentage points]; $P = 0.014$). The median number of unintended breaks lasting 1 minute or more was 2 (interquartile range, 0 to 16) for patients in the interval exercise group and 11 (interquartile range, 2 to 26) for patients in the continuous exercise group ($P = 0.023$).

Limitations: The study focused on initiation of exercise and not on outpatient or home-based maintenance of exercise.

Conclusions: Clinicians and patients can choose either of the 2 exercise plans to initiate physical exercise.

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Low exercise capacity is an important systemic manifestation of advanced chronic obstructive pulmonary disease (COPD) associated with poor health-related quality of life, exacerbations, and death (1–4). Physical exercise, therefore, represents an important element of COPD management (5, 6). If performed under supervision during respiratory rehabilitation, exercise training improves health-related quality of life and may improve prognosis (7–9).

Dyspnea and leg fatigue limit the ability of patients with COPD to exercise, and patient response to exercise is highly variable (10). It is challenging to find endurable exercise programs that are still effective. Current guidelines recommend endurance exercise at constant and high intensity (≥70% of maximum exercise capacity) (11, 12). For example, if a patient achieves 100 watts in an incremental exercise test, workload would be set at 70 watts for the entire exercise session of at least 20 minute's duration. Strong evidence from randomized trials shows that patients achieve clinically important improvements of health-related quality of life and exercise capacity with a continuous exercise protocol (13–16).

However, patients with severe COPD are often unable to tolerate continuous exercise (17), which can be frustrating for them and can limit their long-term adherence to exercise programs. Effective alternatives to continuous exercise are required to offer this important intervention to more patients with COPD. The American Thoracic Society and the European Respiratory Society state, on the basis of 2 randomized trials (18, 19), that interval exercise may be an alternative. The benefits of interval exercise may be similar to those of continuous training, but this method is associated with less dyspnea (11, 12).

Although studies indicated that interval exercise is well tolerated (18–21), evidence about its effectiveness relative to continuous exercise is inconclusive; previous trials had

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Context

Exercise training improves quality of life in patients with chronic obstructive pulmonary disease, but many of these patients cannot tolerate continuous exercise. The effects of intermittent exercise are not known.

Contribution

The authors randomly assigned 100 inpatients with chronic obstructive pulmonary disease in a 3-week respiratory rehabilitation program to receive either high-intensity continuous exercise or high-intensity exercise alternating with low-intensity exercise (interval exercise). After 5 weeks, the 2 groups had similar respiratory symptoms in daily activities and 6-minute walking distance, but the interval exercise group adhered better to the exercise protocol.

Cautions

The study focused on initiation of exercise and not on outpatient or home-based maintenance of exercise.

Implications

For pulmonary rehabilitation, interval exercise is as effective as continuous high-intensity exercise and is better tolerated.

—The Editors

methodological limitations and were small (22). Because of perceived better tolerability of interval exercise, randomized trials should be explicitly designed to show that interval exercise is no less effective (clinical noninferiority) (22). Thus, the aim of our trial was to assess whether interval exercise is no less effective than high-intensity continuous exercise in patients with severe COPD and whether patient tolerance of the interval exercise protocol is superior to that of continuous exercise.

METHODS

Design Overview

We conducted a randomized, controlled noninferiority trial to compare the effects of interval exercise with those of high-intensity continuous exercise in patients with severe COPD. We previously described the detailed study protocol (23) and report this trial following the recommendations of the extended Consolidated Standards of Reporting Trials (CONSORT) statement for noninferiority and equivalence trials (24).

Setting

The trial took place in a public rehabilitation clinic, Klinik Barmelweid, in Aargau, Switzerland. The ethics committee of the Kantonsspital Aarau, Aargau, Switzerland, approved the study protocol, and all study participants provided written informed consent.

Participants

We screened patients admitted to the respiratory medicine unit and included consecutive patients following inclusion criteria similar to those of previous respiratory rehabilitation trials (7): COPD as defined by FEV_1–FVC ratio less than 70% of predicted, FEV_1 less than 50% of predicted after bronchodilation corresponding to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III to IV (5), and German as first or daily language. Exclusion criteria included cardiovascular, musculoskeletal, or neurologic disorders that inhibited physical exercise or the performance of exercise tests (6). We also excluded patients who had received a diagnosis of cancer (excluding skin cancer) within the past 2 years and were undergoing treatment.

Randomization and Interventions

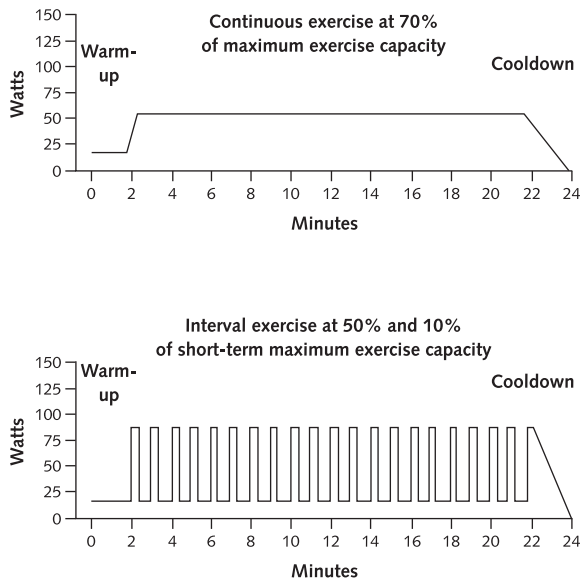
A third party not involved in the execution of the trial (DatInf GmbH, Tuebingen, Germany) provided online central randomization using a computerized minimization procedure, thereby ensuring concealment of randomization (25). Stratification variables were exercise capacity (6-minute walking distance $<$ 300 or $\geq$ 300 meters), the presence of affective disorders (Hospital Anxiety Depression Scale scores $<$ or $\geq$ 8), stability of pulmonary condition (stable or exacerbation within the last 8 weeks), and the need for oxygen at rest (Pa_{O_2} $<$ 55 mm Hg or $\geq$ 55 mm Hg).

Patients followed an inpatient respiratory rehabilitation of approximately 3 week's duration that included 12 to 15 exercise sessions. On weekdays, patients usually participated in 1 exercise session. Twelve physical therapists worked with an approximately equal number of patients from both treatment groups. Apart from exercise, the rehabilitation program was identical for both groups and included breathing therapy, relaxation therapy, guided walking tours, and patient education (23). At discharge, physiotherapists prescribed home-based exercise for each patient. Patients with cycle ergometers at home were instructed to exercise for at least 20 minutes per day. If no cycle ergometers were available, daily walking, swimming, or stair climbing was prescribed.

High-Intensity Continuous Exercise

Patients randomly assigned to this intervention exercised on electromagnetically braked cycle ergometers (Ergometrics 900S, Ergoline, Bitz, Germany) with a target workload of 70% or more of maximum exercise capacity (**Figure 1**). This exercise protocol has been used in earlier respiratory rehabilitation trials (7). To determine maximum exercise capacity, patients pedaled unloaded for 3 minutes at 20 watts to warm up. Then, we used increments of 7.5 watts per minute until patients had to stop because of symptoms or cardiovascular stopping criteria. In each exercise session, patients completed a warm-up period of 2 minutes at 20% of maximum exercise capacity, high-inten-

Figure 1. **Exercise protocols.**



sity exercise for 20 minutes, and a run-out phase of 2 minutes (gradual decrease from 70% to 0%). If patients could not sustain the workload because of perceived dyspnea (modified Borg [26] ratings > 5 on a scale from 0 to 10) or because heart rate exceeded safety limits, physical therapists let patients rest for 1 minute before continuing in the assigned phase. If patients had to rest more than twice per session, physical therapists lowered the workload by steps of 10% of baseline maximum exercise capacity for the following exercise sessions. If workload was too low (modified Borg ratings < 3 or patients or physical therapists considered the workload to be too low), physical therapists increased the workload by steps of 10% of baseline maximum exercise capacity.

Interval Exercise

The target workload for this group was 50% (high-intensity intervals) and 10% (low-intensity intervals) of short-term maximum exercise capacity as determined by a steep ramp test (27, 28). The steep ramp test is an incremental cycle ergometer test in which patients pedal cycle ergometers unloaded for 2 minutes and then at increments of 25 watts every 10 seconds until they cannot maintain a pedaling frequency above 50 pedals per minute or their heart rate exceeds the limit set by the normal incremental exercise test. We used the steep ramp test because workload for interval exercise can be underestimated if it is based on normal incremental exercise tests (28). Fifty percent of short-term maximum exercise capacity corresponds, on average, to 90% to 100% of normal maximum exercise capacity (27). We chose a work–recovery ratio of 1:2 that prevents high lactate accumulation and is well tolerated by patients (28). In each session, patients had a warm-up period of 2 minutes at 10% of the short-term maximum exercise capacity and then exercised for 20 minutes alternating between high-intensity intervals for 20 seconds and low-intensity intervals for 40 seconds (**Figure 1**). Patients also had a slowdown period of 2 minutes before completing the training session. We adjusted the exercise load for each patient individually if workload was too high or too low as described earlier; physiotherapists lowered or increased the workload by steps of 10% of short-term maximum exercise capacity, but the length of intervals remained constant (23).

Outcomes and Measurements

Our primary outcome for effectiveness was the difference from baseline in Chronic Respiratory Questionnaire (CRQ) scores 5 weeks after randomization as measured by the self-administered German-language version (29, 30) with standardized dyspnea questions (31). The CRQ is a widely used instrument in respiratory rehabilitation and measures dyspnea, fatigue, emotional functioning, and ability to cope with COPD (7, 32). Domain and total (average of domains) scores are presented on a Likert-type scale from 1 (most severe impairment) to 7 (no impairment). We selected assessment at 5 weeks after randomization as the primary outcome for the CRQ because the recall period is 2 weeks, and its questions concern impairment associated with activities of daily living in the home environment.

Patients also completed the self-administered German-language version of the Hospital Anxiety Depression Scale, with depression and anxiety domain scores from 0 (no depression or anxiety) to 21 (most severe symptoms of depression or anxiety) (33). In addition, they rated their health state on the feeling thermometer (34), a validated preference-based instrument with marked intervals from 0 (worst health state equals dead) to 100 (perfect health). The feeling thermometer is increasingly being used as a global estimate of the effect of interventions, including respiratory rehabilitation (35, 36).

We used 3 exercise tests to measure changes of exercise capacity. Six-minute walking distance was measured twice at the beginning and once at the end of the inpatient rehabilitation according to established criteria (37). We used the best of the first 2 six-minute walking distances as the baseline value. Patients completed the steep ramp test and an incremental cycle ergometer test to measure anaerobic and aerobic exercise capacity, respectively (23). Physicians from the respiratory medicine unit and physiotherapists from other units of the hospital who supervised these exercise tests were not involved in the supervision of exercise sessions and therefore were blinded to group assignment.

Our primary outcome for tolerance of exercise protocols was the number of unintended breaks lasting 1 or more minutes during the inpatient rehabilitation, which were recorded by physiotherapists on the clinic's routine

exercise diary. In addition, cycle ergometers were connected to a computer to monitor exercise sessions (Ergosofeeling Thermometer Plus, Ergoline-Schiller Reomed AG, Dietikon, Switzerland), and we obtained detailed electronic recordings from each exercise session, including the duration of exercise (in minutes), workload (in watts), and heart rate. We did not compare symptom ratings or heart rate between groups as a measure of exercise tolerance because these variables were used to guide adjustment of exercise intensity and thus were ineligible as outcome measures.

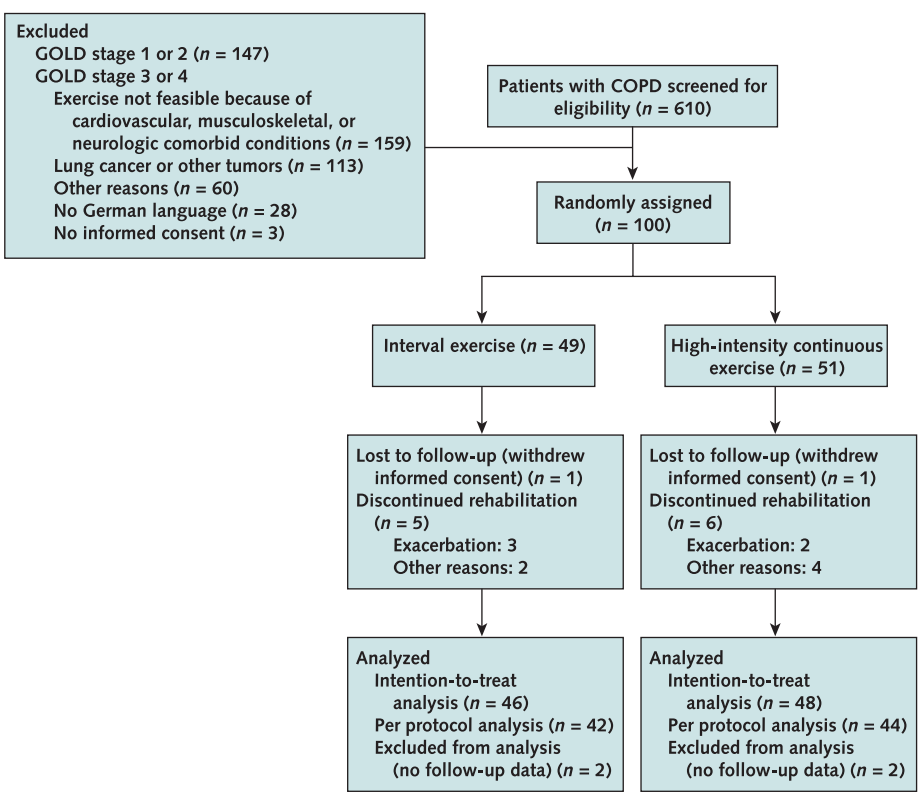
Follow-up Procedures

Patients had a follow-up assessment at the end of the inpatient rehabilitation (after 3 weeks) and after 5 and 12 weeks. The analysis of the CRQ (main outcome), Hospital Anxiety Depression Scale, and feeling thermometer was based on the 5-week assessment during which patients were in their home environment for 2 weeks; analysis of exercise capacity and tolerance was based on the baseline and 3-week follow-up data. A future report focusing on long-term outcomes will include results of the 12-week assessment and 1-year follow-up data.

Statistical Analysis

Data entry and analysis were performed while researchers remained blinded to group assignment (groups were coded as 0 and 1) (38). We used the confidence interval approach as recommended for equivalence and noninferiority trials (39) to compare change scores (difference between baseline and follow-up) between groups. We calculated unadjusted and adjusted (for stratification variables and variables with baseline imbalances) between-group differences with their 95% CIs using linear regression analysis, with change of outcome measures as dependent and group and adjustment variables as independent variables. We established noninferiority of interval exercise when the between-group differences and the lower limits of 95% CIs were above the a priori–determined boundaries of clinical noninferiority, which we set around the minimal important differences (0.5 for CRQ [32], 45 meters for 6-minute walking distance [40], and 8 for the feeling thermometer [41]). The CRQ, 6-minute walking test, and feeling thermometer have served as role models to develop various methods for estimating the minimal important difference. Thus, we were able to set our boundaries of noninferiority according to empirical studies. We used intention-to-treat and per protocol analyses. In equivalence trials, per protocol analysis may be more conservative because it unmasks differences between groups, whereas intention-to-treat analysis may tend to favor equivalence by blurring differences (39, 42–44).

Figure 2. **Study flow diagram.**



COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Table 1. **Baseline Characteristics**

Characteristic	Interval Exercise Group ($n = 48$)	Continuous Exercise Group ($n = 50$)
Age, *y*	69.0 (9.2)	68.9 (9.2)
Male, %	29 (60.4)	36 (72.0)
FEV_1, *L*	0.87 (0.27)	0.89 (0.29)
FEV_1, % *predicted*	34.5 (9.0)	34.1 (8.0)
Mean FEV_1/FVC (SD)*	0.49 (0.19)	0.47 (0.21)
Exacerbation within last 8 wk, %	29 (60.4)	30 (60.0)
PaO_2, *mm Hg*	57.1 (8.9)	59.5 (9.7)
Mean y since diagnosis (SD)*	9.4 (8.4)	9.2 (6.6)
Mean pack y (SD)†	51.4 (31.4)	54.1 (28.3)
Smoking, %	3 (6.3)	6 (12.0)
Mean body mass index (SD)†	25.4 (6.9)	24.0 (5.8)
Chronic Respiratory Questionnaire		
Dyspnea	2.83 (0.90)	3.03 (1.05)
Fatigue	3.63 (1.15)	3.92 (1.28)
Emotional function	3.95 (1.20)	4.12 (1.24)
Mastery	4.03 (1.31)	4.16 (1.34)
Total score	3.61 (0.98)	3.81 (0.98)
Feeling thermometer	53.1 (17.9)	52.9 (18.7)
Hospital Anxiety and Depression Scale		
Depression domain	7.71 (4.03)	7.45 (3.91)
Anxiety domain	7.13 (3.64)	6.81 (4.36)
6-min walking distance, *m*	312.8 (107.9)	332.4 (116.0)
Short-time maximum exercise capacity, *W*	106.3 (48.8)	119.6 (53.5)
Maximum exercise capacity, *W*	53.2 (26.5)	50.6 (19.0)
Medication, %		
Short-acting β-agonist	37 (77.1)	37 (74.0)
Long short-acting β-agonist	44 (91.7)	43 (86.0)
Anticholinergic bronchodilators	26 (54.2)	28 (56.0)
Inhaled steroid	38 (79.2)	39 (78.0)
Oral steroid	27 (56.3)	21 (42.0)
Theophylline	8 (16.7)	7 (14.0)
Antibiotics	12 (25.0)	4 (8.0)
Anabolic steroid	2 (4.2)	1 (2.0)
Comorbid conditions, %		
Cardiovascular	25 (52.1)	32 (64.0)
Endocrine	13 (27.1)	8 (16.0)
Musculoskeletal	7 (14.6)	6 (12.0)

* Data missing for 6 patients (2 in interval and 4 in continuous exercise group).
† Data missing for 3 patients (1 in interval and 2 in continuous exercise group).

Finally, we analyzed exercise tolerance by comparing the number of breaks between groups using the Mann–Whitney U test and the proportion of patients achieving target exercise using the chi-square test.

We handled missing data as follows: If CRQ data were not available at 5-week follow-up, we carried forward the CRQ data from the 3-week follow-up assessment at the end of the inpatient rehabilitation. Data were missing for 6 patients using interval exercise (all were included in per protocol and intention-to-treat analyses) and for 4 patients using continuous exercise (2 were included in the per protocol analysis, and all 4 were included in the intention-to-treat analysis). We did not impute any data if neither the 3-week nor the 5-week assessments were available. The per protocol and intention-to-treat analyses were based on patients with follow-up data. Four patients (2 from each group) had no follow-up data and were excluded from all analyses. In addition, for the per protocol analyses, 1, 1, 2, and 9 patients had missing CRQ, 6-minute walking distance, maximum exercise capacity, and short-term maximum exercise capacity data, respectively. For the intention-to-treat analyses, in addition to the 4 patients without follow-up data, 4, 5, 7, and 13 patients had missing CRQ, 6-minute walking distance, maximum exercise capacity, and short-term maximum exercise capacity data, respectively.

We conducted a sensitivity analysis of the per protocol analysis to test our method of carrying forward CRQ scores from the 3-week assessment to follow-up after 5 weeks for patients with missing values ($n = 8$). We used several imputations with chained equations to predict CRQ total scores after 5 weeks based on available data and repeated the adjusted between-group comparisons (ice and micombine commands of STATA for Windows 8.2, College Station, Texas).

For data on exercise tolerance (breaks and adherence to protocol), physiotherapists completed all exercise protocols. We had computerized recordings for 44 patients using interval exercise and 50 patients using continuous exercise.

We determined that a sample size of 44 patients in each group would show the noninferiority of interval exercise, assuming noninferiority margins of 0.5 in CRQ scores and 45 meters in 6-minute walking distance between groups, with 90% power at a significance level of 5% (1-sided). With an assumed drop-out rate of 15%, the total sample size increased to 104 (23). After 30 participants were enrolled in each arm, we calculated the standard deviation of CRQ scores and found that data met our assumptions. However, we noticed fewer drop-outs than anticipated and, therefore, terminated recruitment after 100 patients. We performed all analyses using SPSS, version 12.0.1 (SPSS, Inc., Chicago, Illinois).

Role of the Funding Sources

AstraZeneca Switzerland, Boehringer Ingelheim Switzerland, and the Klinik Barmelweid provided unrestricted grants for this trial. These funding sources did not have any influence on the planning, conduct, analyses, or publication of the trial or its results.

RESULTS

Between May 2004 and November 2005, 100 of 103 eligible patients agreed to participate in this study (**Figure 2**). One patient in each group withdrew informed consent for unspecified reasons. Forty-three (89.6%) and 44 (88.0%) patients completed the inpatient rehabilitation in the interval and continuous exercise groups, respectively. Eleven patients did not complete the rehabilitation because of COPD exacerbations (3 patients in the interval and 2 patients in the continuous exercise group); musculoskeletal pain (2 patients in the interval and 1 patient in the continuous exercise group); and, in the continuous exercise

Table 2. **Description of Physical Exercise Programs***

Characteristic	Interval Exercise Group (n = 48)	Continuous Exercise Group (n = 50)	Difference	*P* Value
Inpatient rehabilitation				
Median number of exercise sessions (IQR)	13 (12 to 14)	13 (12 to 14)		
Length of individual exercise sessions, *min*	22.5 (2.1)	23.1 (2.8)	−0.6 (−1.6 to 3.8)	0.22
Average workload for all exercise sessions				
High-intensity interval, *W*	50.5 (27.0)			
High-intensity interval, *% of maximum exercise capacity*	98 (37)			
Low-intensity interval, *W*	6.8 (3.4)			
Low-intensity interval, *% of maximum exercise capacity*	14 (6)			
Constant intensity, *W*		30.0 (17.7)		
Constant intensity, *% of maximum exercise capacity*		57 (17)		
Average heart rate for all exercise sessions	106 (13)	109 (14)	−3 (−9 to 4)	0.37
Dyspnea (score 0 to 10)				
After 5 min of exercise	3.2 (1.1)	3.4 (1.3)	−0.2 (−0.7 to 0.3)	0.38
After 20 min of exercise	3.6 (1.0)	3.6 (1.3)	0.0 (−0.5 to 0.5)	0.98
Work, *kJ*				
Per session	25.6 (14.6)	33.5 (25.7)	−7.9 (−16.5 to 0.7)	0.071
Overall	325.8 (20.0)	430.0 (35.3)	−104.2 (−221.7 to 13.4)	0.082
Home-based exercise				
Number of patients with home exercise, %				
No home exercise	14 (29.2)	11 (22.0)		
Any home exercise	36 (70.8)	39 (78.0)		0.42
Unstructured (e.g., walking or swimming)	12 (33.3)	19 (48.7)		
Structured (e.g., cycle ergometer)	24 (66.7)	20 (51.3)		0.176
Median exercise sessions per week (IQR)	5 (1 to 5)	5 (2 to 5)		0.162†
Median total number of exercise sessions 5 wk after randomization (IQR)	22 (14 to 23)	22 (16 to 23)		0.44†

* Values are means (SD) unless otherwise indicated. IQR = interquartile range.
† Mann–Whitney U test.

group only, chest pain, an accident, and newly diagnosed lung cancer.

Table 1 shows the characteristics of study participants at baseline. Sixty percent of patients with COPD were referred after experiencing recent exacerbations, whereas 40% were in stable pulmonary condition. There were more women and more patients with endocrine comorbid conditions (mostly type 2 diabetes) in the interval group, and more patients in the continuous exercise group had cardiovascular comorbid conditions. The number and length of exercise sessions during the inpatient rehabilitation were similar for both groups (**Table 2**). Workload in the interval exercise group averaged 50.5 watts (corresponding to 98% of maximum exercise capacity) for high-intensity intervals. Patients using continuous exercise practiced, on average, at 30.0 watts (57% of maximum exercise capacity). Total work performed was, at borderline statistical significance, higher for the continuous exercise group than for the interval exercise group (430.0 kJ [SD, 35.3] vs. 325.8 kJ [SD, 20.0]). Most patients followed prescribed home exercise, and the average number of total training sessions was 22 after 5 weeks.

Respiratory rehabilitation was effective in both groups, with CRQ change scores similar to those reported in previous rehabilitation trials and exceeding the minimal important difference of 0.5 (**Table 3**). **Figure 3** and **Table 3** show the adjusted between-group comparisons (interval − continuous exercise group) for CRQ scores. On the basis of per protocol analyses, differences between groups were between − 0.08 and − 0.01. Lower limits of the 95% CIs were above the boundary of noninferiority for fatigue, emotional function, mastery domain, and total scores. Lower limits of the 95% CIs just met the minimal important difference of 0.5 for dyspnea scores. The sensitivity analysis with imputed CRQ total scores for patients with missing 5-week follow-up data (derived from several imputations) showed almost identical results (difference between groups, −0.09 [95% CI − 0.48 to 0.30]). Intention-to-treat analyses showed very similar results, and all 95% CIs were above the boundary of noninferiority (**Table 3**).

Improvements in exercise capacity were also substantial for both groups. Increases from baseline to follow-up ranged between 13.3% and 27.7% (**Table 3**). Improvement in 6-minute walking distance was clinically noninferior for the interval exercise group compared with the continuous exercise group (**Figure 4**). Short-term maximum exercise capacity favored interval exercise, whereas changes in maximum exercise capacity were similar for both types of exercise. Changes expressed by the feeling thermometer were also clinically noninferior, and improvements in depression and anxiety symptoms were similar.

Analyses of exercise tolerance were based on intention to treat. Interval exercise was associated with statistically significantly fewer unintended breaks of 1 minute or more.

The median number of unintended breaks during the entire inpatient rehabilitation was 2 (interquartile range, 0 to 16) for the interval exercise group and 11 (interquartile range, 2 to 26) for the continuous exercise group ($P = 0.023$). Patients using interval exercise adhered statistically significantly better to the planned exercise protocol than patients with continuous exercise (47.9% versus 24.0%, difference, 23.9 percentage points [CI, 5.0 to 42.8 percentage points]; $P = 0.014$).

Discussion

This randomized noninferiority trial showed that interval exercise is no less effective than high-intensity continuous exercise for improving health-related quality of life and exercise capacity of patients with severe COPD. Interval exercise, however, was better tolerated, as expressed by fewer breaks and better adherence to exercise protocols.

This randomized trial has several strengths. First, it was designed as a noninferiority trial following rigorous methodological standards, including per protocol and intention-to-treat analyses (39, 42–44). Second, health care staff supervising exercise tests were blinded to group allocation. Third, our trial was larger than all previous trials comparing the 2 exercise programs (18,19, 21) and was sufficiently powered to answer the question of clinical noninferiority. Fourth, we considered important elements of pragmatic trials aimed at informing clinical practice, including comparison of 2 available interventions, enrollment of a high percentage of eligible patients, and use of outcomes important to patients (45).

Implementation of the interventions in clinical practice was associated with some limitations. Our study focused on the difficult initiation of physical exercise for patients with severe COPD during supervised rehabilitation, not on long-term maintenance of exercise programs. Interval and continuous exercise can be performed on any stationary bicycle, but optimal adjustment of exercise load requires supervision. Studies focusing on the transition from supervised rehabilitation programs to home-based or fitness center–based exercise should explore how interval or continuous exercise can be continued in the long term.

Three small trials (18–21) researching interval and continuous exercise published since 1997 were identified by a recent systematic review based on a comprehensive literature search (22). Our data contribute to this litera-

Table 3. **Comparison of Treatment Effects***

Outcome	Per Protocol				Adjusted Difference in Intention-to-Treat Analysis (95% CI)
	Mean Changes from Baseline (SD)		Unadjusted Difference (95% CI)	Adjusted Difference (95% CI)	
	Interval Exercise Group	Continuous Exercise Group			
Primary					
Chronic Respiratory Questionnaire†					
Dyspnea	1.25 (1.19)	1.27 (1.14)	−0.02 (−0.52 to 0.48)	−0.07 (−0.53 to 0.38)	−0.03 (−0.46 to 0.40)
Fatigue	0.94 (1.17)	0.86 (1.36)	0.08 (−0.47 to 0.62)	−0.02 (−0.41 to 0.37)	−0.08 (−0.45 to 0.29)
Emotional function	0.89 (1.02)	0.96 (1.23)	−0.07 (−0.55 to 0.42)	−0.08 (−0.48 to 0.32)	−0.10 (−0.48 to 0.27)
Mastery	0.94 (1.19)	1.00 (1.36)	−0.06 (−0.61 to 0.49)	−0.01 (−0.46 to 0.45)	−0.06 (−0.48 to 0.37)
Total score	1.00 (0.98)	1.02 (1.05)	−0.02 (−0.46 to 0.42)	−0.05 (−0.42 to 0.32)	−0.08 (−0.42 to 0.27)
Secondary					
Exercise tests‡					
6-minute walking distance, *m*	42.3 (64.2)	37.8 (58.2)	4.5 (−21.7 to 30.7)	1.1 (−25.4 to 27.6)	3.4 (−21.7 to 28.6)
6-minute walking distance, %	18.3 (40.0)	13.3 (23.5)	5.0 (−9.0 to 19.0)	1.5 (−11.6 to 14.5)	2.2 (−10.0 to 14.3)
Short-term maximum exercise capacity, *W*	23.8 (32.4)	18.4 (32.3)	5.4 (−9.3 to 20.1)	8.3 (−6.8 to 23.4)	5.6 (−8.4 to 19.5)
Short-term maximum exercise capacity, %	27.7 (41.7)	17.7 (36.1)	10.0 (−7.7 to 27.6)	12.5 (−4.6 to 29.7)	9.0 (−7.3 to 25.3)
Maximum exercise capacity, *W*	8.5 (12.0)	8.7 (10.4)	−0.2 (−4.9 to 4.7)	0.0 (−4.9 to 4.9)	−0.3 (−5.1 to 4.5)
Maximum exercise capacity, %	20.0 (26.2)	16.8 (21.8)	3.2 (−7.1 to 13.5)	2.7 (−8.1 to 13.5)	2.0 (−8.5 to 12.6)
Hospital Anxiety and Depression Scale§					
Depression	2.05 (2.90)	2.93 (2.80)	−0.88 (−2.15 to 0.39)	−0.63 (−1.75 to 0.49)	−0.58 (−1.65 to 0.49)
Anxiety	1.95 (2.22)	2.25 (3.09)	−0.30 (−1.50 to 0.90)	−0.07 (−1.15 to 1.00)	−0.22 (−1.24 to 0.80)
Feeling thermometer‖	10.2 (16.7)	14.5 (14.6)	−4.3 (−11.7 to 3.1)	−0.3 (−7.8 to 3.8)	−0.9 (−6.6 to 4.7)

* Adjusted for sex, 6-minute walk distance, Hospital Anxiety and Depression Scale score, long-term oxygen, recent exacerbation, and cardiovascular and endocrine comorbid conditions, Hospital Anxiety and Depression Scale change scores × −1. Positive numbers represent improvements. The number of patients included in intention-to-treat analyses were 44 for the interval exercise group and 46 for the continuous exercise group for the Chronic Respiratory Questionnaire; 43 and 46 for 6-minute walking distance; 42 and 39 for short-term maximum exercise capacity; 43 and 44 for maximum exercise capacity; 44 and 44 for the Hospital Anxiety and Depression Scale; and 39 and 39 for the feeling thermometer.

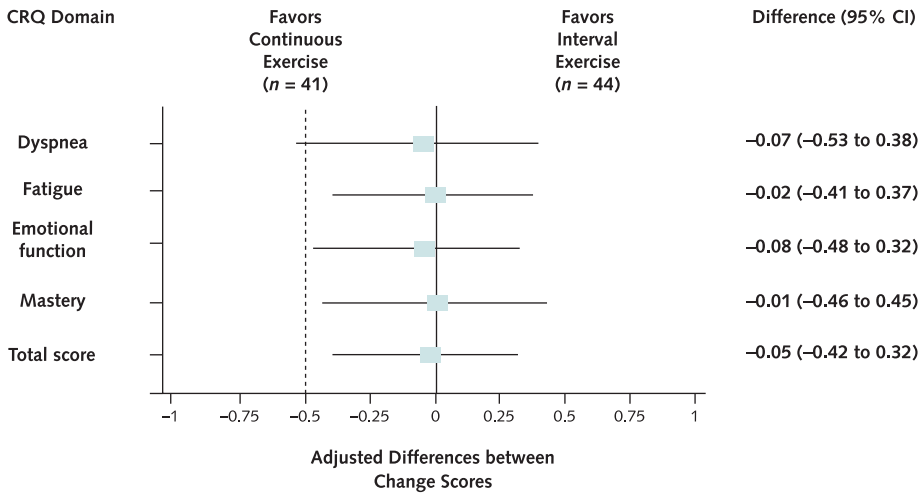
† Number of patients with data for the Chronic Respiratory Questionnaire was 41 for the interval and 44 for the continuous exercise group.

‡ Number of patients with data for the 6-minute walking distance was 41 for the interval and 44 for the continuous exercise group; number of patients with data for short-term maximum exercise capacity was 38 for the interval and 39 for the continuous exercise group; 43 patients in the continuous exercise group had data.

§ Number of patients with depression and number of patients with anxiety who had data was 40 for the interval and 41 for the continuous exercise group.

‖ Number of patients with data for the feeling thermometer was 35 for the interval and 36 for the continuous exercise group.

Figure 3. **Main comparison of health-related quality of life.**

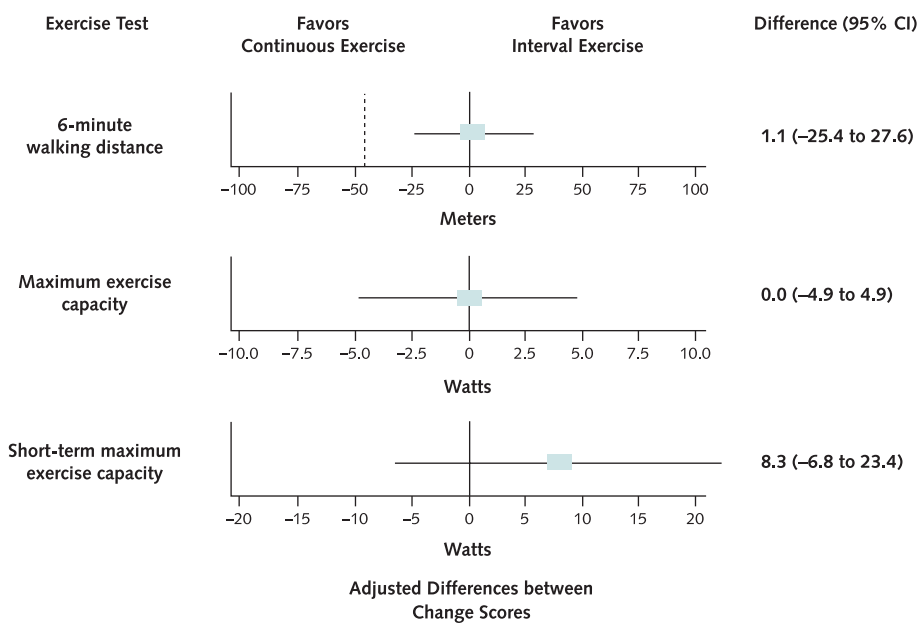


Adjusted for sex, 6-minute walking distance, Hospital Anxiety Depression Scale depression score, long-term use of oxygen, recent exacerbation, and cardiovascular and endocrine comorbid conditions. CRQ = Chronic Respiratory Questionnaire.

ture. The effects of rehabilitation in our trial were similar to those observed in the 3 studies (18–21), which indicated that interval exercise could be an effective and tolerable training alternative. The insignificant differences in those trials, however, did not allow for the conclusion that interval exercise is not clinically inferior to continuous exercise (39, 42–44). In our trial, clinical noninferiority was defined explicitly, and the sample size was large enough to assess whether 95% CIs were above the boundaries of noninferiority.

Although total work was substantially higher for the continuous exercise group, there was no increased benefit.

Figure 4. **Main comparison of exercise capacity.**



Adjusted for sex, 6-minute walking distance, Hospital Anxiety Depression Scale depression score, long-term use of oxygen, recent exacerbation, and cardiovascular and endocrine comorbid conditions. The number of patients included in the per protocol analyses were 41 for the interval exercise group and 44 for the continuous exercise group for the 6-minute walking distance, 38 and 39, respectively, for short-term maximum exercise capacity, and 41 and 43, respectively, for maximum exercise capacity.

Thus, with the same number and duration of exercise sessions as those in the continuous exercise group, patients in the interval exercise group achieved similar improvements in health-related quality of life, the main outcome in respiratory rehabilitation trials, and exercise capacity. This indicates that the short high-intensity stimuli (on average 98% of maximum exercise capacity) were effective in provoking a response similar to that of a constant workload at 57% of maximum exercise capacity. The length of our training session was limited to approximately 25 minutes, a tolerable length for patients with severe COPD. It is possible, however, that patients could endure longer exercise sessions with interval exercise than with continuous exercise, allowing for an increase in training effects (20). This hypothesis needs to be addressed in future studies.

The main CRQ follow-up assessment occurred after 5 weeks because items on the CRQ relate to activities in the home. Patients also completed the CRQ after inpatient rehabilitation (3-week follow-up), and we found even larger changes for the interval exercise group compared with the continuous exercise group (adjusted between-group difference, 0.26 [CI, −0.11 to 0.63] favoring interval exercise). Thus, interval exercise was clearly noninferior at this stage.

Clinicians need to identify patients with COPD who might benefit from respiratory rehabilitation. Some patients can tolerate continuous exercise at high intensity, but our study and another study show that most patients with severe COPD are not able to sustain a continuous exercise protocol (20). For these patients, interval exercise represents an attractive alternative because it offers the same benefit as high-intensity exercise but is better tolerated. Clinicians can choose between interval and continuous exercise to initiate physical activity according to patient preference, allowing a larger proportion of patients with severe COPD to improve their peripheral muscle dysfunction. Our findings strengthen the evidence base for interval exercise and may lead the American Thoracic Society and European Respiratory Society to strengthen their recommendations for this protocol (19).

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References

1. **Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al.** The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005-12. [PMID: 14999112]

2. **Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM, et al.** Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003;58:100-5. [PMID: 12554887]

3. **Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G.** Muscle weakness is related to utilization of health care resources in COPD patients. Eur Respir J. 1997;10:417-23. [PMID: 9042643]

4. **Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R.** Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171:972-7. [PMID: 15665324]

5. Global Initiative for Chronic Obstructive Pulmonary Disease. Guidelines: Workshop Report 2005. Available at www.goldcopd.com/GuidelineItem.asp?intId=1387. Accessed on 16 June 2006.

6. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax. 2004;59 Suppl 1:1-232. [PMID: 15041752]

7. **Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, et al.** Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002:CD003793. [PMID: 12137716]

8. **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. [PMID: 15943867]

9. **Cote CG, Celli BR.** Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J. 2005;26:630-6. [PMID: 16204593]

10. **Troosters T, Gosselink R, Decramer M.** Exercise training in COPD: how to distinguish responders from nonresponders. J Cardiopulm Rehabil. 2001;21:10-7. [PMID: 11271652]

11. American Thoracic Society and European Respiratory Society. Management of stable COPD: pulmonary rehabilitation. Standards for diagnosis and management of patients with COPD. 2004. Accessed at www.ersnet.org/lrPresentations/copd/files/main/index.html on 9 August 2006.

12. Pulmonary rehabilitation-1999. American Thoracic Society. Am J Respir Crit Care Med. 1999;159:1666-82. [PMID: 10228143]

13. **Cambach W, Chadwick-Straver RV, Wagenaar RC, van Keimpema AR, Kemper HC.** The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. Eur Respir J. 1997;10:104-13. [PMID: 9032501]

14. **Wijkstra PJ, Van Altena R, Kraan J, Otten V, Postma DS, Koëter GH.** Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. Eur Respir J. 1994;7:269-73. [PMID: 8162979]

15. **Troosters T, Gosselink R, Decramer M.** Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med. 2000;109:207-12. [PMID: 10974183]

16. **Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al.** Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet. 2000;355:362-8. [PMID: 10665556]

17. **Maltais F, LeBlanc P, Jobin J, Bérubé C, Bruneau J, Carrier L, et al.** Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;155:555-61. [PMID: 9032194]

18. **Coppoolse R, Schols AM, Baarends EM, Mostert R, Akkermans MA, Janssen PP, et al.** Interval versus continuous training in patients with severe COPD: a randomized clinical trial. Eur Respir J. 1999;14:258-63. [PMID: 10515398]

19. **Vogiatzis I, Nanas S, Roussos C.** Interval training as an alternative modality to continuous exercise in patients with COPD. Eur Respir J. 2002;20:12-9. [PMID: 12166558]

20. **Sabapathy S, Kingsley RA, Schneider DA, Adams L, Morris NR.** Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. Thorax. 2004;59:1026-31. [PMID: 15563700]
21. **Kaelin ME, Barnard 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. Presented at the American Society of Exercise Physiologists 2nd Annual Meeting, Indianapolis, Indiana, 1999.
22. **Puhan MA, Schünemann 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;60:367-75. [PMID: 15860711]
23. **Puhan MA, Büsching G, VanOort E, Zaugg C, Schünemann 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 Pulm Med. 2004;4:5. [PMID: 15310394]
24. **Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ, CONSORT group.** Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA. 2006;295:1152-60. [PMID: 16522836]
25. **Pocock SJ, Simon R.** Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975;31:103-15. [PMID: 1100130]
26. **Borg GA.** Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14:377-81. [PMID: 7154893]
27. **Meyer K, Samek L, Schwaibold M, Westbrook S, Hajric R, Beneke R, et al.** Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. Med Sci Sports Exerc. 1997;29:306-12. [PMID: 9139168]
28. **Meyer K, Samek L, Schwaibold M, Westbrook S, Hajric R, Lehmann M, et al.** Physical responses to different modes of interval exercise in patients with chronic heart failure—application to exercise training. Eur Heart J. 1996;17:1040-7. [PMID: 8809522]
29. **Puhan MA, Behnke M, Laschke M, Lichtenschopf A, Brändli O, Guyatt GH, et al.** Self-administration and standardisation of the chronic respiratory questionnaire: a randomised trial in three German-speaking countries. Respir Med. 2004;98:342-50. [PMID: 15072175]
30. **Puhan MA, Behnke M, Frey M, Grueter T, Brandli O, Lichtenschopf A, et al.** 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. [PMID: 14713317]
31. **Schünemann HJ, Goldstein R, Mador MJ, McKim D, Stahl E, Puhan M, et al.** A randomised trial to evaluate the self-administered standardised chronic respiratory questionnaire. Eur Respir J. 2005;25:31-40. [PMID: 15640320]
32. **Schünemann H.** Is there an association between impaired pulmonary function and mortality in never smokers? [Letter] Thorax. 2004;59:81. [PMID: 14694258]
33. **Hinz A, Schwarz R.** [Anxiety and depression in the general population: normal values in the Hospital Anxiety and Depression Scale]. Psychother Psychosom Med Psychol. 2001;51:193-200. [PMID: 11417357]
34. **Bennet K, Torrance GW.** Measuring health state preferences and utilities: rating scale, time trade-off, and standard gamble techniques. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott–Raven; 1996:253-66.
35. **Schünemann HJ, Griffith L, Stubbing D, Goldstein R, Guyatt GH.** A clinical trial to evaluate the measurement properties of 2 direct preference instruments administered with and without hypothetical marker states. Med Decis Making. 2003;23:140-9. [PMID: 12693876]
36. **Puhan MA, Behnke M, Devereaux PJ, Montori VM, Braendli O, Frey M, et al.** Measurement of agreement on health-related quality of life changes in response to respiratory rehabilitation by patients and physicians—a prospective study. Respir Med. 2004;98:1195-202. [PMID: 15588040]
37. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111-7. [PMID: 12091180]
38. **Gøtzsche PC.** Blinding during data analysis and writing of manuscripts. Control Clin Trials. 1996;17:285-90; discussion 290-3. [PMID: 8889343]
39. **Jones B, Jarvis P, Lewis JA, Ebbutt AF.** Trials to assess equivalence: the importance of rigorous methods. BMJ. 1996;313:36-9. [PMID: 8664772]
40. **Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH.** Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med. 1997;155:1278-82. [PMID: 9105067]
41. **Schünemann HJ, Griffith L, Jaeschke R, Goldstein R, Stubbing D, Guyatt GH.** Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol. 2003;56:1170-6. [PMID: 14680667]
42. **Fleming TR.** Design and interpretation of equivalence trials. Am Heart J. 2000;139:S171-6. [PMID: 10740126]
43. **Greene WL, Concato J, Feinstein AR.** Claims of equivalence in medical research: are they supported by the evidence? Ann Intern Med. 2000;132:715-22. [PMID: 10787365]
44. **McAlister FA, Sackett DL.** Active-control equivalence trials and antihypertensive agents. Am J Med. 2001;111:553-8. [PMID: 11705432]
45. **Tunis SR, Stryer DB, Clancy CM.** Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA. 2003;290:1624-32. [PMID: 14506122]

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