

TITLE: Randomized controlled trial of exercise training in chronic respiratory failure due to kyphoscoliosis

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ABSTRACT

Background: Research has provided evidence for the safety, feasibility, and efficacy of exercise training in patients with chronic obstructive pulmonary disease. However, little is known about the impact of exercise training in patients with chronic respiratory failure due to kyphoscoliosis. The objective of the current study was to evaluate the effect of an exercise training program on exercise capacity, muscle strength, dyspnea and quality of life indices, in patients with chronic respiratory failure due to kyphoscoliosis. .

Methods: Clinically stable patients with chronic respiratory failure due to kyphoscoliosis (n=34), receiving home mechanical ventilation during the night for the previous six months, were randomly assigned to an exercise (n = 17) or control (n = 17) group. The exercise group trained three non-consecutive days per week for 12 weeks, including cycle and strength exercises. The study outcomes were changes in pulmonary function, exercise capacity, peripheral muscle strength, dyspnea scores, and quality of life from baseline to post-intervention.

Results: Statistical analysis was carried out in 16 patients in the exercise group and in 11 patients in the control group. Lung function parameters did not change from baseline to post-intervention, with the exception of arterial carbon dioxide (p = 0.04), inspiratory (p = 0.025) and expiratory pressures (p = 0.04). In the exercise group, endurance time (p=0.002) and shuttle walking distance (p=0.001) increased significantly. Improvements occurred in the exercise group in peripheral muscle strength, dyspnea, and quality of life were statistically different when compared to the control group.

Conclusions: In patients with chronic respiratory failure due to kyphoscoliosis, exercise training had beneficial effects on exercise capacity and peripheral muscle strength, resulting in less dyspnea and better quality of life.

Key words: chronic respiratory failure, exercise training, kyphoscoliosis, peripheral muscle strength, quality of life, dyspnea, endurance capacity, pulmonary rehabilitation.

INTRODUCTION

Patients with severe kyphoscoliosis (KS) are at increased risk of developing respiratory failure. Although, this is multifactorial, and mainly caused by both changes in the mechanical properties of the rib cage and reduced lung compliance. The magnitude of the restrictive lung disorder seems to be related to the severity of the deformity.¹

Patients with KS usually show oxyhaemoglobin desaturations during exercise,² associated with impaired exercise capacity and disabling breathlessness.³ A number of factors may contribute to reduced exercise capacity in patients with KS. Hamilton et al. (1995) found a significant association between peripheral muscle strength (PMS) and exercise parameters in subjects with chronic respiratory diseases, including KS.⁴ Latest data by Swallow et al. (2009) have revealed quadriceps dysfunction in patients with advanced scoliosis.⁵

When KS is complicated by chronic respiratory failure, the prognosis gets worse. However, survival may be improved using non-invasive mechanical ventilation that enhances gas exchange efficiency and alleviates symptoms of chronic alveolar hypoventilation.⁶ Unfortunately, both exercise limitation and dyspnea usually become persistent over time determining impaired health-related quality of life (HRQL).⁷

In patients with chronic obstructive pulmonary disease (COPD), exercise training (ET) is recognized as an evidence-based treatment in improving exercise capacity, muscle strength, dyspnea, and HRQL.⁸ Recently, significant benefits of a 24-week pulmonary rehabilitation program have been reported in a heterogeneous group of patients with restrictive lung diseases, some of them diagnosed with KS.⁹ However, less is known about the impact of ET in patients with chronic respiratory failure due to kyphoscoliosis (KS-CRF). Because of the multiple beneficial effects of exercise training, this approach could theoretically be a useful tool. Thus, we investigated whether an exercise program combining strength and endurance training had the potential to improve exercise capacity, muscle strength, and clinical symptoms in patients with KS-CRF.

METHODS

This study was designed as a randomized controlled trial. Thirty-four KS-CRF patients (16 males and 18 females; mean age: 62.5 ± 9.5 years) were enrolled in this study. The aetiology of KS was idiopathic in 15 patients (45.8%), Pott's disease in 11 cases (33.3%), post-polio in 3 patients (8.3%), post-traumatic in 3 cases (8.3%), and skeletal malformations in 2 patients (4.2%). Eligibility criteria included (a) being an

adult diagnosed as having KS-CRF and receiving home mechanical ventilation (HMV) during the night for at least the last six months, and (b) being in clinically stable conditions for at least the last three months. CRF was defined as a condition in which patients had an arterial oxygen tension (PaO₂) < 60mmHg and/or arterial carbon dioxide tension (PaCO₂) > 45 mmHg. Eligible participants were not admitted if they had any contraindication or inability to perform any of the study tests (uncontrolled heart disease, acute pulmonary disease, and other conditions). After baseline assessments, patients were allocated to one of the two study arms (exercise group or control group) using a computer generated randomization list". A total of 17 patients were allocated to each arm. The sequence was concealed until interventions were assigned. All subjects used bi-level positive airway pressure ventilation (BIPAP; Respironics Inc. Murrysville, PA, USA) and took medication as usual. Along the period study, participants in the control group were only scheduled for baseline and final evaluation visits.

Ethics approval for the trial was received from the local Institutional Review Board (*Comité Etico de Investigación Clínica; CEIC*) and all enrolled patients provided written informed consent at trial onset.

The trial was registered at DRKS (DEUTSCHEN REGISTER KLINISCHER STUDIEN) .Registration number: DRKS00000443

Training protocol

Subjects trained three non-consecutive days per week for 12 weeks, in the Pulmonary Rehabilitation Unit of our Hospital. A supervised session lasted approximately 60 min, and included a 10-min period of proper warm-up and stretching. Patients combined 30-min leg exercise on a calibrated ergo cycle (Ergometer ZX1; Kettler Sport, Ense-Parsit, Germany) with five weight-lifting exercises for the major muscles of the upper and lower body. The work rate corresponding to 70% of the baseline peak workload was selected as the target training intensity. The strength-training program was performed as previously described.¹⁰ *Patients were administered supplemental oxygen during training, if necessary to maintain oxygen saturation above 90%.*

Measurement tools

Subjects were evaluated at baseline and after 12 weeks of training. Pre- and postexercise tests were performed under similar conditions. The following measurements were obtained from each subject: (1) pulmonary function tests ; (2) shuttle walking test (SWT); (3) endurance test; (4) maximal cycle exercise test; (5) PMS; (6) HRQL; and (7) dyspnea. Our primary outcomes were changes in endurance and SWT.

Pulmonary function tests

Spirographic studies were carried out on a Masterlab pneumotachograph spirometer (Erich Jaeger GMBH, Wuerzburg Germany) following the SEPAR¹¹ and ATS¹² recommendations.

Exercise testing

Cardiopulmonary exercise test (CPET) was performed on a cycle ergometer (Collins Respiratory Ergometer, Braintree, MA, USA) as previously described¹³ and according to the international standards.¹⁴ After two days, a cycling test was performed at a constant workload of 70% of the maximum achieved during the initial CPET, to obtain the endurance time. Post endurance perceived dyspnea was assessed using a modified Borg's scale.¹⁵ Following a two-hour rest, the shuttle walking test was conducted as described by Singh et al.¹⁶ Maximum level reached and distance covered in meters were collected.

Respiratory and peripheral muscle strength

Maximum inspiratory mouth pressures (MIP) from residual volume (RV) and maximum expiratory mouth pressures (MEP) from total lung capacity (TLC) were calculated using a manometer (model 163; Silbelmed, Barcelona, Spain). Reference values used to report these results were those by Morales et al.¹⁷ One repetition maximum (1RM) tests were used for measuring PMS.¹⁸ This test measures the maximum amount of weight (in kilos) that could be lifted in a single movement using a multigym station (Fitness Classic Centre, Kettler, Postfach, Germany). Five simple exercises (chest pull, butterfly, shoulder press, leg extension and leg curls) engaging very large muscle masses (both in lower and upper limbs) were selected.

Dyspnea scales

Basal dyspnea was measured using the Basal Dyspnea Index/Transitional Dyspnea Index (BDI/TDI),¹⁹ and the modified Medical Research Council scale (MRC).²⁰ The BDI/TDI is a multidimensional instrument for measuring dyspnea which includes three domains (functional impairment, magnitude of task, and magnitude of effort) that are graded from -3 to +3, where -1 to -3 signifies deterioration, 0 signifies no change, and 1 to 3 signifies improvement (the change in 1 U has been thought to imply clinical significance).²¹ The MRC dyspnea scale is a set of five statements about dyspnea. The subject is asked to select the statement that most closely applies.

Health-related quality of life (HRQL)

The Chronic Respiratory Disease Questionnaire (CRDQ), Spanish validated version,^{22,23} was used to assess HRQL. This instrument is comprised of four scores: dyspnea, fatigue, emotional function, and

mastery measured on a 7-point scale, with a score of 7 indicating no health impairment consequently, the higher the score, the better the quality of life. Change of 0.5 U has been identified as the minimum clinically significant change.

Statistical analysis

The trial was designed to demonstrate the benefits of ET on exercise, muscle strength, dyspnea and quality of life parameters. The sample size was calculated based on the workload increase in the CPET in a prior study.¹⁰ Considering a 10 W increase and +/- 5 W as the SD, a sample size of 30 patients (15 per group) was necessary to detect a significant difference in this measure between groups, with a power of 90% and an α error of 0.05 using a two-tailed test. Assuming 15% lost to follow-up, we planned the inclusion of 34 patients. Data are presented as means and standard deviations (SD). Kolmogorov-Smirnov test revealed skewed distribution in all continuous variables. Thus, nonparametric statistical procedures were used for data analysis. Within-group comparisons of outcome measures were done by the Wilcoxon test. We used the Mann-Whitney U test to compare changes between groups in outcomes from baseline to post intervention. SPSS software (version 14.0, SPSS Inc, Chicago, IL, USA) was used for all calculations. Differences were considered statistically significant at two-tailed $p < 0.05$.

RESULTS

Figure 1 shows the flow of participants through the trial. A total of 34 KS-CRF patients were initially included in the study. Patients exhibited a severe deformity ranging 90-130 (26)^o of scoliosis and 92-125 (34)^o kyphosis. In the exercise group (n = 17), one patient died of infection-related acute respiratory failure. In the control group (n = 17), one patient died of acute respiratory failure, one patient experienced a stroke, and 4 patients dropped out due to lack of motivation. Therefore, statistical analysis for efficacy was carried out in 16 patients in the exercise group and in 11 patients in the control group. Patients did not experience any important complication during or from the exercise program and completed 82% of the training sessions. Table 1 presents the baseline characteristics. There were no significant differences between groups for any of the baseline measurements. All patients showed severe pulmonary function impairment, that did not change after the study intervention, except for PaCO₂, which significantly decreased [from 48.4 (4.6) to 47.2 (5.1) mmHg; $p = 0.04$].

Changes in exercise capacity. Table 2 lists the exercise capacity outcomes. There were no significant changes in VO_{2max} or W_{max} in either group at the end of the study. Similarly, increases in these parameters

were not different between groups.

The mean distances walked in the SWT increased significantly in the exercise group (mean increase: 67.2 m, $p=0.001$) but not in the control group (mean increase: 23.3 m, $p=0.08$). Greatest increases were observed in cycle endurance time in trained patients, with a mean increase of 12.2 minutes, $p=0.002$ (Table 2). Despite this, changes were not different between groups ($p=0.41$)

No differences from baseline to post-intervention were noted in either group with regard to exertion dyspnea and leg discomfort.

Changes in respiratory and peripheral muscle strength. MIP and MEP increased significantly, from 38 (7) to 41.3 (8)%; $p=0.025$, and from 48 (12) to 52.3 (6) $p=0.04$; respectively. Figure 2 and Table 3 show the PMS outcomes. Average 1RM for all exercises increased significantly in the exercise group and in comparison to the control group. Statistically significant increases in the control group were observed only for the chest pull and butterfly exercises.

Changes in breathlessness and HRQL Table 4 lists the breathlessness and quality of life outcomes.

Changes observed were significantly different between groups. The mean mMRC dyspnea score decreased significantly in the exercise group [-0.5 (0.6); $p=0.02$]. Meaningful improvements in dyspnea (i.e., TDI focal score 1 unit) were seen for all dimensions [magnitude of task: +1.8 (1.1), functional impairment: +1.6 (1.2), magnitude of effort +1.6 (1.2); $p < 0.05$]. Overall HRQL and its dimensions (dyspnea, fatigue, and emotional function) increased significantly in the exercise group. In the control group, there was no improvement in either dyspnea or HRQL.

DISCUSSION

To our knowledge, this is the first randomized controlled trial to investigate the effects of exercise training combining endurance and strength in patients with KS-CRF. In support of our hypotheses, we found that ET had beneficial effects on exercise capacity and peripheral muscle strength, resulting in less dyspnea and better quality of life, exceeding changes observed in the control group. One of the strengths of the current study is its design, which was randomized, prospective and controlled, differing from recent research;⁹ conversely, a limitation is the small sample size and its heterogeneity, explained by the difficulties associated with recruiting participants with KS-CRF condition, which has a low incidence.

Lung function and respiratory muscle strength. Pulmonary rehabilitation does not directly improve lung mechanics or gas exchange. Our intervention did not produce a change in lung function parameters, the only exceptions being a decrease in PaCO₂. Few data are available as to the effects of ET in patients with chronic respiratory failure (CRF).²⁴ A multicentre Italian study has recently investigated the impact of ET in COPD patients with and without CRF.²⁵ After training, patients with CRF showed a highly significant reduction in mean PaCO₂ (-3.3 mmHg). The magnitude of this change is more than double than that observed in our study (-1.2 mmHg), but it was similarly significant. In patients with KS, previous studies have shown an inverse correlation between PaCO₂ and MIP,²⁶ indicating that impairment of inspiratory muscle function may lead to respiratory failure. The better inspiratory muscle function after ET is likely to be associated with improved thoracic mobility. Additional improvements in dynamic ventilatory mechanics may reduce microatelectasis, resulting in increased elastic recoil of the lung and improved PaCO₂ exchange. Our finding that respiratory muscle strength consistently increased suggests that not only the muscles of the shoulder girdle, which contribute to pulmonary ventilation, but also inspiratory muscles were overloaded sufficiently during the course of upper-extremity training.

Exercise tolerance. Despite appropriate medical treatment and home mechanical ventilation, our patients were severely impaired. We found that exercise training did not improve significantly VO_{2max} or W_{max}, but this result was expected given the high degree of respiratory impairment. Intriguingly, W_{max} increased by 30% in the exercise group. The magnitude of this treatment effect is higher than the reported mean increase – 18% – after COPD rehabilitation.²⁷ Lower limb strength training and cycling may account for this beneficial effect. Another main finding of our trial was that cycling endurance time and level and distance walked in the SWT improved significantly in the exercise group. These results are of interest

since endurance – rather than strength – is important for activities of daily living. Exercise training was associated with a 112% improvement in cycle endurance performance. The magnitude of this change is similar to those reported in COPD patients, who generally show greater improvements in constant work rate tests.²⁷ It is noteworthy that SWT has been validated to be sensitive to assess functional capacity in patients with kyphoscoliosis.²⁸ Interestingly, the mean distance walked in SWT increased 67.2 m in the exercise group, exceeding the 47.5 m that is considered to be the minimum clinically important difference after pulmonary rehabilitation.²⁹ Part of these increases might account for to a learning effect, given the smaller yet non-significant increases also observed in the control group, for both tests.

Peripheral muscle strength. Abnormalities of the peripheral muscle play a crucial role in exercise intolerance in patients with chronic respiratory diseases.^{4,30} However, peripheral muscle strength is not routinely measured in patients with KS-CRF. In our group of patients, low values for strength measures were obtained in line with results reported in a very recent research, which has provided important data documenting weakness and fibre-type changes of the quadriceps muscle in this kind of patients.⁵ These data confer additional rationale for the muscle training in KS-CRF.

In our KS-CRF patients, the magnitude of changes in PMS ranged between 29.6% and 64.2% , and were significantly greater in the training group. This percentage improvement is consistent with a growing body of research showing that exercise training improves PMS in patients with restrictive lung diseases.

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Dyspnea and HRQL. The results of this trial demonstrate that exercise training improves dyspnea ratings. Further studies are needed to explore factors contributing to dyspnea in this patient group. We have previously shown that both respiratory muscle strength and PMS may influence dyspnea perception and exercise capacity in KS-CRF patients.³² It is therefore reasonable to assume that amelioration of PMS contributed to the improved patient perception of breathing. A change of at least 1 unit in TDI has been used as the criterion for a minimal important meaningful difference.²¹ The improvement in BDI/TDI and in each of the three components of the TDI focal score in the exercise group can thus be considered a clinically significant change.

Peripheral muscle strength, dyspnoea and exercise capacity have been identified as having independent effects on HRQL in KS-CRF patients.³³ Our patients had an impaired HRQL, with lower scores on the dyspnea and fatigue dimensions. An important finding of our trial was that exercise training had a

beneficial effect on overall HRQL. In addition, there were significant improvements in 3 of the 4 dimensions of the CRDQ that exceeded the minimum important difference of 0.5 points,³⁴ and significantly surpassing changes in the control group. No changes were observed in the mastery score from baseline to post-intervention. This finding may be due to the fact that the patients included in the study were in a stable state under optimal medical therapy.

Limitations of the study: As stated before, some limitations stand up in the present study. The small sample size and its heterogeneity may account for the lack of significant differences between training and control groups in terms of exercise capacity. Evaluation of long-term benefits could have provided us with additional valuable information on that issue. The control group didn't have the same number of visits as the training group and this may explain the important dropout rate among these patients.

Conclusions: Collectively, our results demonstrate the safety, feasibility, and efficacy of ET in patients with KS-CRF. Benefits obtained are in line with those previously reported in observational studies,^{9,35} despite our patients being in a more severe clinical situation. The intervention consisted of a complete simultaneous training for both strength and endurance, causing beneficial effects on exercise capacity, muscle strength, dyspnea and HRQL. This approach may help define the optimal content of pulmonary rehabilitation programs for this kind of patients. In summary, our findings if replicated, suggest that exercise training should be recommended to KS-CRF patients receiving nocturnal home mechanical ventilation.

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Figure legends

Figure 1 Flow of participants through the trial.

Figure 2 Muscle Strength results (1RM test), baseline and at 12-weeks, in both groups

Legend to Figure 2: The numbers above the bars represent the percent of increase only for statistically significant differences.

TABLES

Table 1 Baseline characteristics of the study participants

	Exercise group (n = 16)	Control group (n = 11)	p
Sex, males/female	7/9	6/5	0.8
Age, years	61.1 (9.0)	63.9 (9.1)	0.39
HMV- <i>t</i> , months	18.4(5)	17.8(3)	0.5
FVC, % pred	31.8 (9.6)	35.7 (12.0)	0.36
FEV ₁ , % pred	29.3 (9.6)	30.7 (9.6)	0.87
FEV ₁ /FVC %	75.8 (12.0)	71.6 (14.4)	0.26
FRC, % pred	53.9 (21.4)	54.2 (16.7)	0.64
RV, % pred	59.4 (14.8)	59.7 (15.9)	0.89
TLC, % pred	40.8 (9.6)	43.4 (15.0)	0.25
PaO ₂ , mmHg	64.9 (9.2)	64.1 (18.0)	0.74
PaCO ₂ , mmHg	48.4 (4.6)	45.1 (5.6)	0.35
MIP, cmH ₂ O	37 (10.4)	36.4 (9.5)	0.83
% pred	38 (7)	36.9(6)	
MEP, cmH ₂ O	75.3 (23.1)	86 (35.4)	0.64
% pred	48 (12)	54 (14)	

Data are given as mean (SD) or counts, as appropriate.

HMV-*t*, time on home mechanical ventilation; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; % pred, % predicted; PaO₂, arterial oxygen pressure; PaCO₂, arterial carbon dioxide pressure; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.

Table 2 Effects of exercise training on exercise capacity outcomes

	Exercise group (n = 16)			Control group (n = 11)			Inter-group comparison
	Baseline	Post intervention	p	Baseline	Post intervention	p	
VO ₂ max % pred	50.5 (12.2)	52.4 (18.3)	0.97	46.7 (12.2)	47.2 (12.6)	0.63	0.8
Wmax % pred	20.6 (15.9)	26.8 (20.3)	0.16	17.4 (16.4)	19.6 (22.8)	0.12	0.3
SWT, meters	187.5 (116.7)	259.6 (118.1)	0.001	229.3 (98.4)	255.0 (125.5)	0.08	0.06
SWT, level	4.4 (1.8)	5.5 (1.6)	0.007	5.3 (1.4)	5.2 (1.9)	0.89	0.073
Dyspnea-SWT	8.7 (0.8)	8.1 (1.9)	0.8	8.7 (0.9)	8.3 (1.2)	0.9	0.9
Endurance time, min	10.7 (15.4)	22.7 (20.3)	0.002	11.7 (18.9)	18.5 (22.8)	0.4	0.41
Endurance -dyspnea	8.0 (1.9)	6.6 (2.9)	0.7	7.5 (2.7)	7.4 (2.0)	0.8	0.73

Data are given as mean (SD).

VO₂max, maximum oxygen uptake; Wmax, maximum power; SWT, shuttle walking test, expressed either in meters or as level; Dyspnea-SWT, dyspnea in SWT (Borg's scale); Endurance time, time in endurance test (minutes); Endurance-dyspnea, dyspnea (Borg's scale) in endurance test.

p value represents the within-group comparison with Wilcoxon test.

Inter-group comparison: *p* values for Mann-Whitney U test to compare changes between groups.

Table 3. Effects of exercise training on peripheral muscle strength (1RM test)

	Exercise group (n = 16)			Control group (n = 11)			<i>Inter-group comparison</i>
	Baseline	Post-intervention	p	Baseline	Post-intervention	p	
Chest pull	26(7.5)	33.7(9.3) [†]	0.001	25.7(7.6)	27.5(8.7)	0.042	0.013
Butterfly	9.2(5.2)	14(8) [†]	0.001	10.9(6.3)	11.7(7.4)	0.042	0.02
Shoulder press	15.1(8.7)	19.9(10.8) [†]	0.001	15.3(4.9)	16.7(6.8)	0.09	0.006
Leg extension	24.4(10.7)	37(13.3) [†]	0.000	21.7(7.1)	25.1(7.9)	0.09	0.005
Leg flexion	8.4(5.1)	13.8(4.5) [†]	0.012	10.1(5)	11.2(4.5)	0.086	0.016

Data are given as mean (SD).

The 1RM (one repetition maximum test) results are expressed in kilos.

p value represents the within-group comparison with Wilcoxon test being $p < 0.05$ statistically significant ; Inter-group comparison: p values for Mann-Whitney U test to compare changes between groups; [†] $p < 0.05$; [‡] $p < 0.005$

Table 4 Effects of exercise training on dyspnea and quality of life outcomes

	Exercise group (n = 16)			Control group (n = 11)			<i>Inter-group comparison</i>
	Baseline	Post intervention	p	Baseline	Post intervention	p	
MRC score	3.8 (0.9)	3.2 (0.8) [†]	0.020	3.7 (1.1)	3.5 (1.1)	0.9	0.045
BDI/TDI-MT	1.1 (0.6)	+1.8 (1.1) ^{*‡}	0.020	1.4 (0.8)	+0.2 (0.4)	0.45	0.002
BDI/TDI-FI	1.2 (0.6)	+1.6 (1.2) ^{*†}	0.040	1.6 (1.2)	+0.2 (0.4)	0.6	0.012
BDI/TDI- ME	1.1 (0.6)	+1.6 (1.2) ^{*†}	0.020	1.5 (0.8)	+0.1 (1.2)	0.83	0.005
BDI/TDI focal score	4.6 (2.5)	+5.0 (3.3) ^{*‡}	0.015	3.6 (1.9)	+0.3 (1.9)	0.57	0.003
CRDQ-Dyspnea	2.7 (0.9)	3.7 (0.9) ^{*†}	0.003	2.7 (0.7)	2.9 (0.5)	0.54	0.026
CRDQ-Fatigue	3.7 (0.8)	4.7 (1.0) ^{*†}	0.005	4.1 (1.3)	4.6 (1.1)	0.64	0.014
CRDQ-EF	4.4 (0.9)	5.1 (1.0) ^{*†}	0.013	4.6 (1.4)	5.0 (1.6)	0.09	0.011
CRDQ-Mastery	5.0 (1.2)	5.6 (0.9)	0.09	4.5 (1.6)	5.4 (1.1)	0.08	0.549
CRDQ-Global	12.1 (2.0)	15.0 (2.8) ^{*†}	0.005	12.7 (2.9)	13.9 (2.9)	0.07	0.018

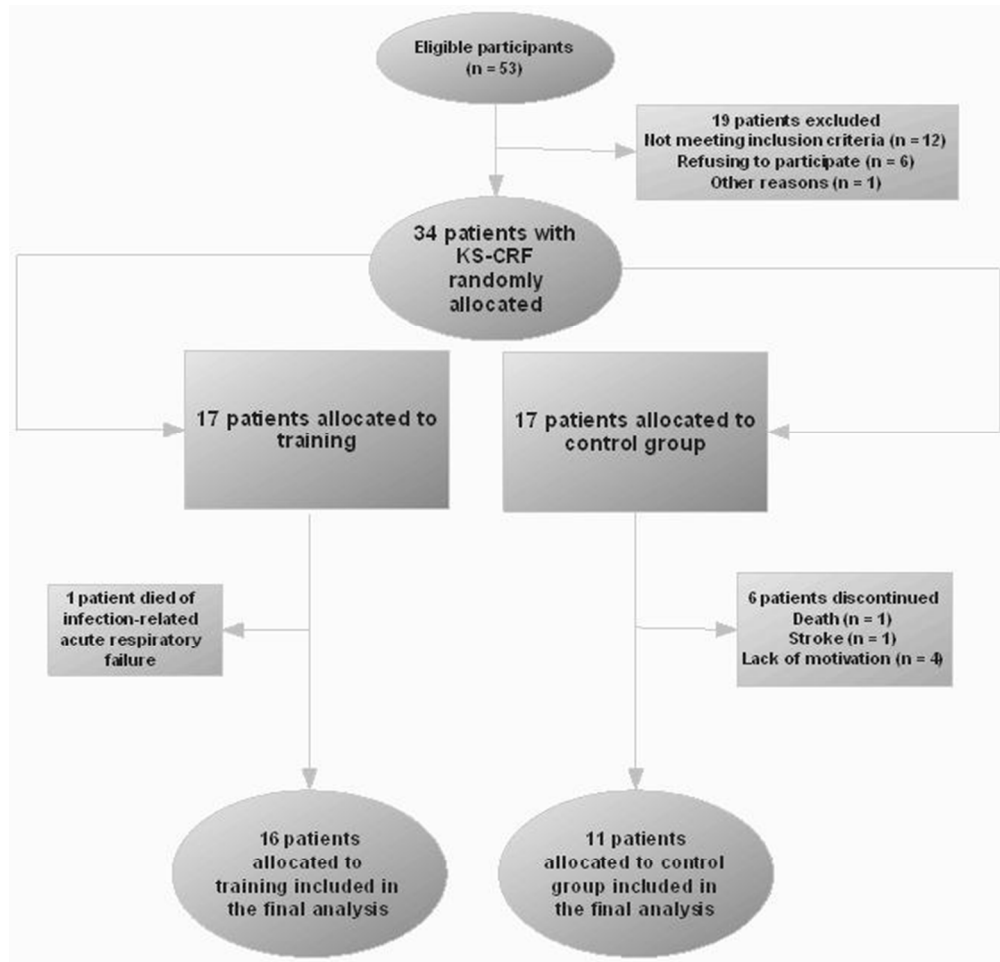
Data are given as mean (SD).

MRC, modified Medical Research Council dyspnea scale. BDI/TDI, Basal dyspnea index (MT, magnitude of task; FI, functional impairment; ME, magnitude of effort); CRDQ-EF, emotional function.

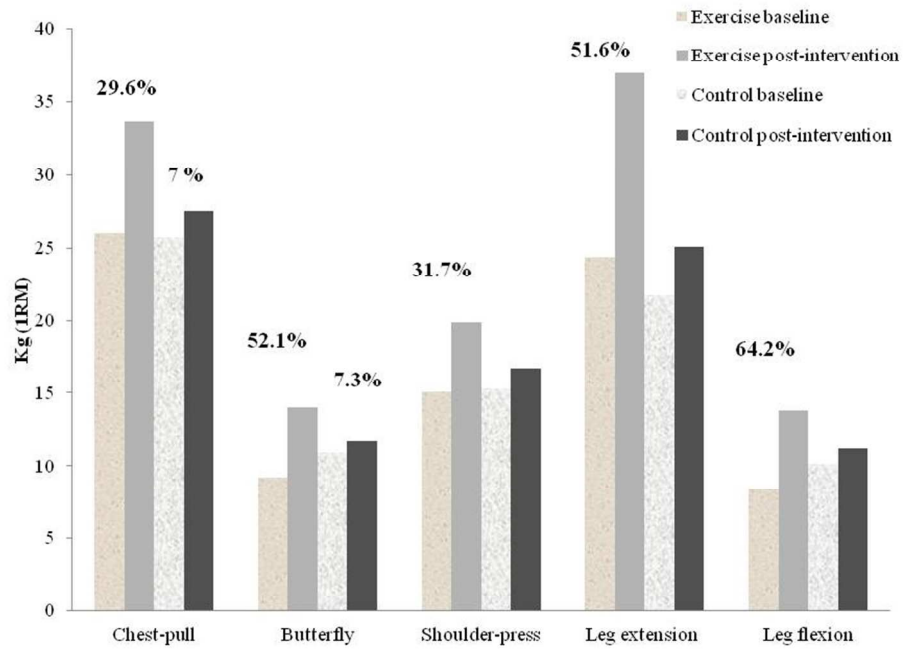
p value represents the within-group comparison with Wilcoxon test; *clinically significant change (+ 0.5 points increase in the CRDQ questionnaire).

Inter-group comparison: p values for Mann-Whitney *U* test to compare changes between groups;

[†]*p*<0.05; [‡]*p*<0.005



176x169mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)