Exercise Training in Patients With Chronic Respiratory Failure Due to Kyphoscoliosis: A Randomized Controlled Trial

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BACKGROUND: Research has provided evidence for the safety, feasibility, and efficacy of exercise training in patients with COPD. However, little is known about the impact of exercise training in patients with chronic respiratory failure due to kyphoscoliosis. We evaluated the effect of an exercise training program on exercise capacity, muscle strength, dyspnea, and quality-of-life indices in subjects with chronic respiratory failure due to kyphoscoliosis. METHODS: The 34 subjects were clinically stable, had been receiving nighttime home mechanical ventilation for ≥ 6 months, and were randomly assigned to the exercise group (*n* = 17) or the control group (*n* = 17). The exercise group conducted cycle and strength training on 3 non-consecutive days per week for 12 weeks. We measured pulmonary function, exercise capacity, peripheral muscle strength, dyspnea scores, and quality of life. RESULTS: Statistical analysis was carried out on the data from 16 subjects in the exercise group and in 11 subjects in the control group. Three of the lung-function parameters in the exercise group significantly changed: P_{aCO_2} (*P* = .04), inspiratory pressure (*P* = .03), and expiratory pressure (*P* = .04); and endurance time (*P* = .002) and shuttle walk distance (*P* = .001) increased significantly. The exercise group had significantly greater improvements in peripheral muscle strength, dyspnea, and quality of life. CONCLUSIONS: In patients with chronic respiratory failure due to kyphoscoliosis, exercise training improved exercise capacity, peripheral muscle strength, dyspnea, and quality of life. (Deutschen Register Klinischer Studien DRKS00000443) *Key words: chronic respiratory failure; exercise training; kyphoscoliosis; peripheral muscle strength; quality of life; dyspnea; endurance capacity; pulmonary rehabilitation.* [Respir Care 2014;59(3):375–382. © 2014 Daedalus Enterprises]

Introduction

Patients with severe kyphoscoliosis (KS) are at risk of developing respiratory failure, mainly due to changes in the mechanical properties of the rib cage and reduced lung compliance. The magnitude of the lung restriction seems to be related to the severity of the deformity.[1]

Patients with KS usually show oxyhemoglobin desaturation during exercise,[2] which is associated with impaired exercise capacity and disabling dyspnea.[3] Several factors contribute to reduced exercise capacity in patients with KS. Hamilton et al (1995) found a significant association between peripheral muscle strength and exercise parameters in subjects with chronic respiratory diseases, including KS.[4] Swallow et al (2009) found quadriceps dysfunction in patients with advanced KS.[5]

When KS is complicated by chronic respiratory failure, the prognosis gets worse. However, survival may be improved with noninvasive ventilation, which enhances gas exchange efficiency and alleviates alveolar hypoventilation.[6] Unfortunately, both exercise limitation and dyspnea

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usually become persistent and impair health-related quality of life (HRQL).[7]

In patients with COPD, exercise training is recognized as an evidence-based treatment in improving exercise capacity, muscle strength, dyspnea, and HRQL.[8] Recently, significant benefits from a 24-week pulmonary rehabilitation program were reported in a heterogeneous group of patients with restrictive lung diseases, some with KS.[9] However, less is known about the impact of exercise training in patients with chronic respiratory failure due to KS (KS-CRF). In patients with KS-CRF we investigated an exercise program that included strength and endurance training.

QUICK LOOK

Current knowledge

Exercise training in a pulmonary rehabilitation program improves quality of life in patients with COPD. The impact of exercise training on patients with kyphoscoliosis and restrictive lung disease is not well described.

What this paper contributes to our knowledge

In patients with chronic respiratory failure due to kyphoscoliosis, exercise training improved exercise capacity, peripheral muscle strength, dyspnea, and quality of life.

Methods

This randomized controlled trial was approved by the institutional review board of, and conducted at, Hospital Universitario Virgen del Rocío, Sevilla, Spain. All subjects gave written informed consent before enrollment. We enrolled 34 KS-CRF patients: 16 males, 18 females, mean age 62.5 ± 9.5 years. The etiology of KS was idiopathic in 15 subjects (45.8%), Pott disease in 11 subjects (33.3%), post-polio in 3 subjects (8.3%), post-traumatic in 3 subjects (8.3%), and skeletal malformation in 2 subjects (4.2%). We included adults with KS-CRF, receiving nighttime home mechanical ventilation for ≥ 6 months, and who had been clinically stable for ≥ 3 months. Our definition of CRF included $P_{aO_2} < 60$ mm Hg and/or $P_{aCO_2} > 45$ mm Hg. We excluded patients who had any contraindication to any study procedure or were unable to perform any of the study tests (eg, uncontrolled heart disease or acute pulmonary disease). After baseline assessments the subjects were randomly allocated to the exercise group or the control group, using a computer-generated randomization list. Seventeen subjects were allocated to each group. The sequence was concealed until interventions were assigned. All the subjects used noninvasive ventilation (BIPAP, Respironics, Murrysville, Pennsylvania) and took their usual medications. The control subjects were only scheduled for the baseline and final evaluation visits.

Training Protocol

The exercise-group subjects trained 3 non-consecutive days per week for 12 weeks, in our hospital's pulmonary rehabilitation unit. The exercise sessions were supervised, lasted approximately 60 min, and included a 10-min period of warm-up and stretching. The sessions included a 30-min period of leg exercise on a calibrated ergometer cycle (ZX1, Kettler Sport, Ense-Parsit, Germany) and 5 weight-lifting exercises for the major upper and lower body muscles. The target training intensity was 70% of the baseline peak work load. The strength-training program was performed as previously described.[10] The subjects were administered supplemental oxygen during training, if necessary to maintain oxygen saturation above 90%.

Measurement Protocol

The subjects were evaluated at baseline and after 12 weeks of training. The baseline and post-intervention tests and assessments were performed under similar conditions. Each subject underwent pulmonary function tests, shuttle walk test, endurance test, maximal cycle exercise test, peripheral muscle strength tests; HRQL assessment, and dyspnea assessment. Our primary outcomes were changes in endurance and shuttle walk test results.

Pulmonary Function Tests

Spirometry (Masterlab, Erich Jaeger, Friedberg, Germany) was per the Sociedad Española de Neumología y Cirugía Torácica (SEPAR)[11] and American Thoracic Society[12] recommendations.

Exercise Testing

Cardiopulmonary exercise testing was performed with a cycle ergometer (Ergomed, Collins Respiratory, Braintree, Massachusetts) as previously described,[13] and according to the international standards.[14] After 2 days a cycling test was performed at a constant work load of 70% of the maximum achieved during the initial cardiopulmonary exercise test, to obtain the endurance time. Post-endurance-test dyspnea was assessed with the modified Borg scale.[15] Following a 2-hour rest, the shuttle walk test was conducted, as described by Singh et al,[16] and we recorded the maximum level reached and the distance covered.

Respiratory and Peripheral Muscle Strength

Maximum inspiratory pressure, measured at the mouth, starting from residual volume, and maximum expiratory pressure, measured at the mouth, starting from total lung capacity, were measured (163, SibelMed, Barcelona, Spain) and analyzed with the reference from Morales et al.[17] One-repetition maximum tests were used for measuring peripheral muscle strength.[18] This type of test measures the maximum amount of weight that can be lifted in a single movement, using a multi-station weightlifting machine (Fitness Classic Centre, Kettler, Postfach, Germany). Five simple exercises (chest pull, butterfly, shoulder press, leg extension and leg curls) engaging the largest muscles of the lower and upper limbs were selected.

Dyspnea

Baseline dyspnea was measured with the Baseline Dyspnea Index/Transitional Dyspnea Index,[19] and the modified Medical Research Council dyspnea scale.[20] The Baseline Dyspnea Index/Transitional Dyspnea Index has 3 domains (functional impairment, magnitude of task, and magnitude of effort) that are graded from -3 to 3, where scores in the range -1 to -3 signify deterioration, 0 signifies no change, and scores in the range 1 to 3 signify improvement. A 1-unit is thought to imply clinical importance.[21] The modified Medical Research Council dyspnea scale is a set of 5 statements about dyspnea. The subject is asked to select the statement that most closely applies.

Health-Related Quality of Life

The Chronic Respiratory Disease Questionnaire, Spanish validated version,[22,23] was used to assess HRQL. This instrument has 4 domains (dyspnea, fatigue, emotional function, and mastery), each of which is measured on a 7-point scale, and a score of 7 indicates no health impairment; consequently, the higher the score, the better the quality of life. A change of 0.5 unit is considered the minimum clinically important change.

Statistical Analysis

The trial was designed to determine the effects of exercise training on exercise, muscle strength, dyspnea, and quality-of-life parameters. The sample size was calculated based on the work load increase in the cardiopulmonary exercise test in a prior study.[10] Considering a 10-Watt increase and ± 5 Watts as the standard deviation, a sample size of 30 subjects (15 per group) was necessary to detect a significant difference between the groups, with a power of 90% and an α error of .05, using a 2-tailed test. Assuming 15% lost to follow-up, we planned to enroll 34 subjects. Data are presented as mean ± SD. The Kolmogorov-Smirnov test revealed skewed distribution in all the continuous variables, so nonparametric statistical procedures were used for the data analysis. Within-group comparisons of outcome measures were done with the Wilcoxon test. We used the Mann-Whitney U test to compare changes between groups. We used statistics software (SPSS 14.0, SPSS, Chicago, Illinois) for all calculations. Differences were considered statistically significant when the 2-tailed P was $< .05$.

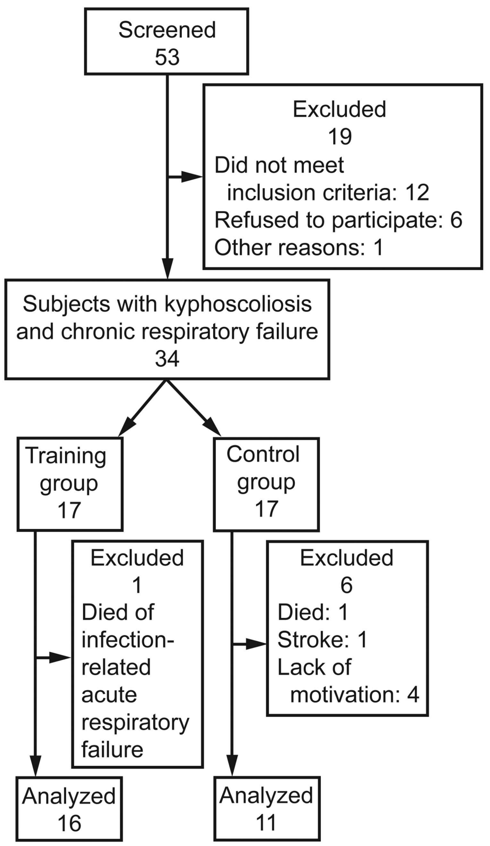

Fig. 1. Flow chart.

Results

Figure 1 shows the flow chart. A total of 34 KS-CRF subjects were initially included. The subjects exhibited a severe deformity: range 90–130° (26 subjects) of scoliosis, and 92–125° (34 subjects) of kyphosis. In the exercise group ($n = 17$) one subject died of infection-related acute respiratory failure. In the control group ($n = 17$) one subject died of acute respiratory failure, one subject had a stroke, and 4 subjects dropped out due to lack of motivation. Therefore, statistical analysis was carried out on the data from 16 subjects in the exercise group and 11 subjects in the control group. None of the exercise subjects had any important complications during or from the exercise program, and they completed 82% of the training sessions. Table 1 presents the baseline characteristics. There were no significant differences between the groups in any of the

Table 1. Baseline Characteristics

	Exercise Group (n = 16)	Control Group (n = 11)	P
Male/female, no.	7/9	6/5	.80
Age, y	61.1 ± 9.0	63.9 ± 9.1	.39
Months on home mechanical ventilation	18.4 ± 5	17.8 ± 3	.50
FVC, % predicted	31.8 ± 9.6	35.7 ± 12.0	.36
FEV_1, % predicted	29.3 ± 9.6	30.7 ± 9.6	.87
FEV_1/FVC, %	75.8 ± 12.0	71.6 ± 14.4	.26
Functional residual capacity, % predicted	53.9 ± 21.4	54.2 ± 16.7	.64
Residual volume, % predicted	59.4 ± 14.8	59.7 ± 15.9	.89
Total lung capacity, % predicted	40.8 ± 9.6	43.4 ± 15.0	.25
P_{aO_2}, mm Hg	64.9 ± 9.2	64.1 ± 18.0	.74
P_{aCO_2}, mm Hg	48.4 ± 4.6	45.1 ± 5.6	.35
Maximum inspiratory pressure, cm H_2O	37 ± 10.4	36.4 ± 9.5	.83
Maximum inspiratory pressure, % predicted	38 ± 7	36.9 ± 6	
Maximum expiratory pressure, cm H_2O	75.3 ± 23.1	86 ± 35.4	.64
Maximum expiratory pressure, % predicted	48 ± 12	54 ± 14	

Values are mean ± SD unless otherwise indicated.

Table 2. Exercise Capacity Before and After Training

	Exercise Group (n = 16)			Control Group (n = 11)			P for Inter-Group Comparison†
	Baseline	Post-intervention	P*	Baseline	Post-intervention	P*	
Maximum $\dot{V}_{O_2}$, % predicted	50.5 ± 12.2	52.4 ± 18.3	.97	46.7 ± 12.2	47.2 ± 12.6	.63	.80
Maximum work, % predicted	20.6 ± 15.9	26.8 ± 20.3	.16	17.4 ± 16.4	19.6 ± 22.8	.12	.30
Shuttle walk distance, m	187.5 ± 116.7	259.6 ± 118.1	.001	229.3 ± 98.4	255.0 ± 125.5	.08	.06
Shuttle walk test level	4.4 ± 1.8	5.5 ± 1.6	.007	5.3 ± 1.4	5.2 ± 1.9	.89	.07
Dyspnea score during shuttle walk test	8.7 ± 0.8	8.1 ± 1.9	.80	8.7 ± 0.9	8.3 ± 1.2	.90	.90
Endurance cycle time, min	10.7 ± 15.4	22.7 ± 20.3	.002	11.7 ± 18.9	18.5 ± 22.8	.40	.41
Dyspnea score during endurance test	8.0 ± 1.9	6.6 ± 2.9	.70	7.5 ± 2.7	7.4 ± 2.0	.80	.73

Values are mean ± SD.
* Via Wilcoxon test.
† Via Mann-Whitney U test.
$\dot{V}_{O_2}$ = oxygen uptake

baseline measurements. All the subjects had severe pulmonary function impairment, and the only variable that significantly changed after the study intervention was P_{aCO_2}, which decreased from 48.4 ± 4.6 mm Hg to 47.2 ± 5.1 mm Hg (P = .04).

Changes in Exercise Capacity

Table 2 lists the exercise capacity outcomes. There were no significant changes in maximum $\dot{V}_{O_2}$ or maximum work in either group after the exercise program. Similarly, the increases in maximum $\dot{V}_{O_2}$ or maximum work were not significantly different between the groups.

The mean distance walked in the shuttle walk test increased significantly in the exercise group (mean increase 67.2 m, P = .001) but not in the control group (mean increase 23.3 m, P = .08). The greatest increase was in cycle endurance time in the exercise-group subjects (mean increase 12.2 min, P = .002, see Table 2). Despite this, the changes were not significantly different between the groups (P = .41). There was no significant post-intervention change in dyspnea or leg discomfort in either group.

Changes in Respiratory and Peripheral Muscle Strength

Maximum inspiratory pressure and maximum expiratory pressure increased significantly, from 38 ± 7% to 41.3 ± 8% (P = .03), and from 48 ± 12% to 52.3 ± 6% (P = .04), respectively. Figure 2 and Table 3 show the

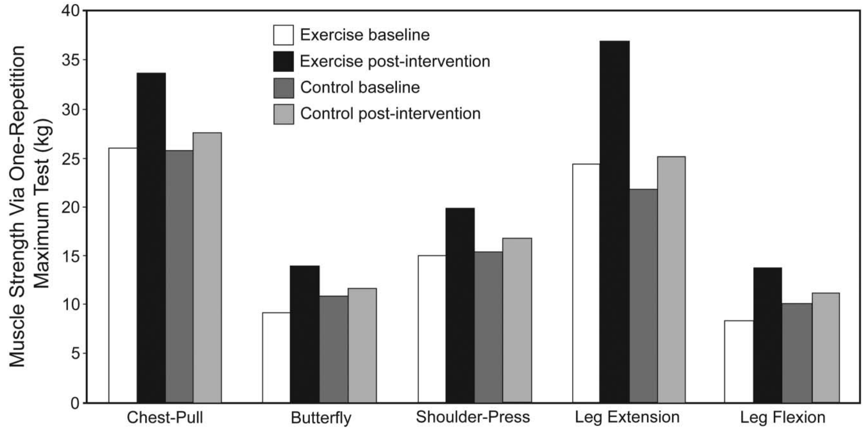

Fig. 2. Muscle strength at baseline and after a 12-week exercise training program.

Table 3. Peripheral Muscle Strength Before and After Training

	Exercise Group, kg ($n = 16$)			Control Group, kg ($n = 11$)			P for Inter-Group Comparison†
	Baseline	Post-intervention	P*	Baseline	Post-intervention	P*	
Chest pull	26 ± 7.5	33.7 ± 9.3‡	.001	25.7 ± 7.6	27.5 ± 8.7	.042	.01
Butterfly	9.2 ± 5.2	14 ± 8‡	.001	10.9 ± 6.3	11.7 ± 7.4	.042	.02
Shoulder press	15.1 ± 8.7	19.9 ± 10.8‡	.001	15.3 ± 4.9	16.7 ± 6.8	.09	.006
Leg extension	24.4 ± 10.7	37 ± 13.3‡	< .001	21.7 ± 7.1	25.1 ± 7.9	.09	.005
Leg flexion	8.4 ± 5.1	13.8 ± 4.5‡	.01	10.1 ± 5	11.2 ± 4.5	.09	.02

Values are mean ± SD.
* Via Wilcoxon test.
† Via Mann-Whitney U test.
‡ $P < .05$.

peripheral muscle strength outcomes. The average one-repetition maximum for all exercises increased significantly in the exercise group, and in comparison to the control group. The control group had statistically significant increases only in the chest pull and butterfly exercises.

Changes in Dyspnea and HRQL

Table 4 lists the dyspnea and quality of life outcomes. The changes were significantly different between the groups. The mean modified Medical Research Council dyspnea score decreased significantly in the exercise group, by 0.5 ± 0.6 units ($P = .02$). There were meaningful improvements in all the Transitional Dyspnea Index domains: magnitude of task 1.8 ± 1.1 units, functional impairment 1.6 ± 1.2 units, magnitude of effort 1.6 ± 1.2 units (all $P < .05$). The global score of the HRQL questionnaire and 3 of 4 of its existing domains (dyspnea, fatigue, and emotional function) increased significantly in the exercise group. In the control group there was no improvement in dyspnea or HRQL.

Discussion

To our knowledge, this is the first randomized controlled trial to investigate the effects of exercise training that combined endurance and strength in subjects with KS-CRF. In support of our hypotheses, we found that exercise training improved exercise capacity, peripheral muscle strength, dyspnea, and quality of life, whereas there were no significant changes in the control group. One of the strengths of the current study is its design, which was randomized, prospective, and controlled, in contrast to previous research.[9] Conversely, a limitation of the present study is the small sample size and its heterogeneity, which is explained by the difficulty in recruiting patients with a rare condition such as KS-CRF.

Lung Function and Respiratory Muscle Strength

Pulmonary rehabilitation does not directly improve lung mechanics or gas exchange. Our intervention changed only one lung function parameter: P_{aCO_2}. Few data are available on the effects of exercise training in patients with chronic

Table 4. Dyspnea and Quality of Life Before and After Training

	Exercise Group (n = 16)			Control Group (n = 11)			P for Inter-Group Comparison†
	Baseline	Post-intervention	P*	Baseline	Post-intervention	P*	
Dyspnea score	3.8 ± 0.9	3.2 ± 0.8‡	.02	3.7 ± 1.1	3.5 ± 1.1	.90	.045
Baseline Dyspnea Index/Transitional Dyspnea Index domain							
Magnitude of task	1.1 ± 0.6	+1.8 ± 1.1§‖	.02	1.4 ± 0.8	+0.2 ± 0.4	.45	.002
Functional impairment	1.2 ± 0.6	+1.6 ± 1.2§‡	.04	1.6 ± 1.2	+0.2 ± 0.4	.60	.01
Magnitude of effort	1.1 ± 0.6	+1.6 ± 1.2§‡	.02	1.5 ± 0.8	+0.1 ± 1.2	.83	.005
Focal score	4.6 ± 2.5	+5.0 ± 3.3§‖	.02	3.6 ± 1.9	+0.3 ± 1.9	.57	.003
Chronic Respiratory Disease Questionnaire domain							
Dyspnea	2.7 ± 0.9	3.7 ± 0.9§‡	.003	2.7 ± 0.7	2.9 ± 0.5	.54	.03
Fatigue	3.7 ± 0.8	4.7 ± 1.0§‡	.005	4.1 ± 1.3	4.6 ± 1.1	.64	.01
Emotional function	4.4 ± 0.9	5.1 ± 1.0§‡	.01	4.6 ± 1.4	5.0 ± 1.6	.09	.01
Mastery	5.0 ± 1.2	5.6 ± 0.9	.09	4.5 ± 1.6	5.4 ± 1.1	.08	.55
Global	12.1 ± 2.0	15.0 ± 2.8§‡	.005	12.7 ± 2.9	13.9 ± 2.9	.07	.02

Values are mean ± SD.
* Via Wilcoxon test.
† Via Mann-Whitney U test.
‡ $P < .05$.
§ Clinically important change (0.5 point increase in Chronic Respiratory Disease Questionnaire domain score).
‖ $P < .005$.

respiratory failure.[24] A multi-center Italian study recently investigated the impact of exercise training in COPD patients with and without chronic respiratory failure.[25] After training, the subjects with chronic respiratory failure had significantly reduced mean P_{aCO_2} (−3.3 mm Hg). The magnitude of that change is more than double that observed in our study (−1.2 mm Hg), but it was similarly significant. In subjects with KS, previous studies have found an inverse correlation between P_{aCO_2} and maximum inspiratory pressure,[26] indicating that impairment of inspiratory muscle function may lead to respiratory failure. The improved inspiratory muscle function after exercise training is probably associated with improved thoracic mobility. Additional improvements in dynamic ventilatory mechanics may reduce microatelectasis, resulting in increased elastic recoil of the lung and improved P_{aCO_2}. 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 the inspiratory muscles were overloaded sufficiently during the course of upper-extremity training.

Exercise Tolerance

Despite appropriate medical treatment and home mechanical ventilation, our subjects were severely impaired. We found that exercise training did not significantly improve maximum $\dot{V}_{O_2}$ or maximum work, but this result was expected, given our subjects' high degree of respiratory impairment. Intriguingly, maximum work 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 is that cycling endurance time and shuttle walk test level and distance 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. The magnitude of that change is similar to the change reported in COPD patients, who generally show greater improvements in constant work rate tests.[27] It is noteworthy that the shuttle walk test has been validated to be sensitive to assess functional capacity in patients with KS.[28] Interestingly, the mean shuttle walk distance increase was 67.2 m in the exercise group, which exceeds 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 a learning effect, given the smaller yet nonsignificant increases also observed in the control group, for both tests.

Peripheral Muscle Strength

Abnormalities of the peripheral muscles play a crucial role in exercise intolerance in patients with chronic respiratory disease.[4,30] However, peripheral muscle strength is not routinely measured in patients with KS-CRF. Our subjects had low strength measurements, which is in line with the results of a recent study that provided important data documenting weakness and fiber-type changes in the quadriceps muscle in patients with scoliosis.[5] These data support the rationale for muscle training in patients with KS-CRF.

In our KS-CRF subjects the magnitude of changes in peripheral muscle strength ranged between 29.6% and 64.2%, and were significantly greater in the exercise group. This improvement is consistent with a growing body of research showing that exercise training improves peripheral muscle strength in patients with restrictive lung diseases.[9,31]

Dyspnea and HRQL

Our results demonstrate that exercise training improves dyspnea. Further studies are needed to explore factors contributing to dyspnea in KS-CRF patients. We previously found that both respiratory muscle strength and peripheral muscle strength affect dyspnea and exercise capacity in KS-CRF subjects.[32] It is therefore reasonable to assume that improved peripheral muscle strength contributed to the improved patient perception of breathing. A change of 1 unit in the Transitional Dyspnea Index is considered the minimum clinically important difference.[21] The improvement in Baseline Dyspnea Index/Transitional Dyspnea Index and in all 3 domains of the Transitional Dyspnea Index in the exercise group can thus be considered a clinically important change.

Peripheral muscle strength, dyspnea, and exercise capacity have independent effects on HRQL in KS-CRF patients.[33] Our subjects had impaired HRQL, with lower scores on the dyspnea and fatigue dimensions. An important finding of our trial was that exercise training improved the overall HRQL score. In addition, there were significant improvements in 3 of the 4 domains of the Chronic Respiratory Disease Questionnaire, that exceeded the minimum important difference of 0.5 point,[34] and significantly surpassed the changes in the control group. There was no significant post-intervention change in the mastery domain score, which may be due to the fact that our subjects were stable and under optimal medical therapy.

Limitations

Our small sample size and its heterogeneity may account for the lack of significant differences in exercise capacity between the training and control groups. Evaluating long-term benefits might have provided additional valuable information on that issue. Also, the control group didn't have the same number of visits as the exercise group, which may explain the substantial drop-out rate in the control group.

Conclusions

Collectively, our results demonstrate the safety, feasibility, and efficacy of exercise training in patients with KS-CRF. The benefits we obtained are in line with those previously reported in observational studies,[9,35] despite that our subjects were more severely ill. Our exercise intervention consisted of a complete simultaneous training for both strength and endurance, which improved exercise capacity, muscle strength, dyspnea, and HRQL. This approach may help define the optimal content of pulmonary rehabilitation programs for KS-CRF patients. In summary, our findings suggest that exercise training should be recommended to KS-CRF patients receiving nighttime home mechanical ventilation.

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