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Original Research

Is exercise and electrostimulation effective in improving muscle strength and cardiorespiratory fitness in children with cystic fibrosis and mild-to-moderate pulmonary impairment?: Randomized controlled trial

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ABSTRACT

Background: Evidence on resistance-training programs for cystic fibrosis (CF) is limited and the possible benefits of the addition of neuromuscular electrical stimulation (NMES) are unknown. This study aimed to evaluate the effects of a supervised resistance-training program, associated or not with NMES, on muscle strength, aerobic fitness, lung function and quality of life in children with CF presenting mild-to-moderate pulmonary impairment.
Methods: This is a randomized controlled trial including CF patients aged between 6 and 17years. Subjects were randomly allocated to control (CON); exercise (EX); or exercise and NMES (EX + NMES) groups, and evaluated at baseline and at the end of an 8-week individualized exercise-program (3 days/week, 60min/session). NMES was applied in the quadriceps and the interscapular region, simultaneously to the exercises. CON group followed the CF team recommendations. The main outcome measures were lung function, cardiorespiratory fitness, functional capacity, quality of life and muscle strength.
Results: Twenty-seven patients, aged 12.6 ± 3.0 years, were analyzed. No significant interactions were found for cardiorespiratory fitness. Functional capacity presented significant differences, indicating a better performance in both EX and EX + NMES. No significant changes between groups were seen for quality of life and lung function. As for muscle strength, EX and EX + NMES presented large effect sizes and significant differences, compared to CON, for quadriceps ($p = 0.004$, $\eta^2_p = 0.401$), pectoral ($p = 0.001$, $\eta^2_p = 0.487$), dorsal ($p = 0.009$, $\eta^2_p = 0.333$) and handgrip ($p = 0.028$, $\eta^2_p = 0.278$).
Conclusion: A resistance exercise-training program led to improvements in muscle strength and functional capacity in CF patients with mild-to-moderate pulmonary impairment. The addition of NMES to the training program resulted in no extra favorable effects.

1. Introduction

Cystic fibrosis (CF) is a hereditary, autosomal recessive disease, caused by the mutation of a gene that encodes the transmembrane conductance regulator protein (CFTR), affecting the chloride transport in all epithelial cells [1]. The absence or dysfunction of the protein leads to a multisystemic disease, inducing obstruction in secretory glands [2].

Therefore, excess mucous production and dysfunctions in the lungs, liver, pancreas, and reproductive organs occur, leading to impaired pulmonary function, suboptimal absorption of nutrients, and frequent bacterial infection [3]. Although a significant degree of phenotypic variability exists between individuals, the most important cause of morbidity and mortality is associated to respiratory failure, which accounts for almost 95% of deaths [4,5]. CFTR is also an important

regulator of cellular inflammatory homeostasis, and its absence has been found to be associated with increased nuclear factor kappa B (NF-kB), leading to chronic inflammation and excessive inflammatory responses [6]. In addition, several other tissues are affected, including the skeletal muscle [7], in which alterations in the oxidative metabolism [8], calcium homeostasis [9], increased proteolysis [10], and altered muscle contractility and fatigability [11] have been reported. Recent evidence has also shown altered peripheral (muscular) oxygen supply, as well as the ability to efficiently extract and use oxygen at the myocyte level [12, 13], which consists in a major determinant of exercise intolerance. As a consequence, these alterations lead to a greater degree of fatigue both at central (any structure above the neuromuscular junction) and local levels (at or distal to the neuromuscular junction) [7], intolerance to exercise [14], decreased muscle strength [7], and more hospitalizations [15].

Lower aerobic fitness is associated with an increased risk of hospitalization for pulmonary exacerbations [15], a poorer quality of life [16], and a worse prognosis [17]. The study of Hebestreit et al. [18] confirms the importance of the peak oxygen consumption (VO_2peak) and peak work rate as key predictors of survival, although it also identifies other cardiopulmonary exercise testing (CPET) variables (peak V_E/VO_2 and V_E/VCO_2) that may be of prognostic significance. The use of cluster analysis also suggests phenotypes of risk, for which early recognition, nutritional counseling and exercise intervention could be beneficial [18]. Pathogenesis of exercise limitation in the CF population is multifactorial, including alterations in cardiovascular, muscular and respiratory systems [12–14,16]. Considering the endocrine function of peripheral muscles in regulating cytokines production and release [19], therapeutic strategies to reduce systemic inflammation, muscle catabolism and improve muscle function are of great importance and exercise at the appropriate dose can be an useful tool to maintain molecular signaling [20], leading to beneficial muscular adaptations.

On the other hand, the evidence on the efficacy of physical exercise training in CF is still limited, especially by the sample size of existing trials [21]. Although exercise takes part of the routine care offered to most CF patients, evidence on prescription of individualized training doses and specific exercise modalities are still highly needed. Neuromuscular electrical stimulation (NMES) is a useful tool to prevent muscle atrophy and reduced mobility resulting from chronic diseases [22,23]. The use of NMES for children with neuromuscular diseases has been effective in improving strength, cardiovascular capacity, bone mineralization, and functional mobility [24–26]. However, evidence for the use of NMES in CF is still scarce. The use of NMES prior to resistance training for severe pulmonary dysfunction CF patients was useful to increase peripheral muscle strength, contributing to improve body weight, quality of life and reduce the ventilation requirements during exercise [22].

Therefore, considering the limited evidence on the use of resistance-training programs for patients with CF, as well as the possible benefits of adding NMES, this study aimed to evaluate the effects of a supervised resistance-training program, associated or not with NMES, on muscle strength, aerobic fitness, lung function and quality of life in children with CF presenting mild-to-moderate pulmonary impairment.

2. Methods

2.1. Study design

This is a randomized controlled trial following the recommendations of the Consolidated Standards of Reporting Trials statement [27]. It was carried out in a tertiary children Hospital (Niño Jesus, Madrid, Spain) following all principles described in the Declaration of Helsinki. The study was approved by the Hospital Research Ethics Committee (R-0019/18), as well as registered on ClinicalTrials.gov (NCT04153669). All legal guardians and patients over 12 years signed an informed consent to participate in the study.

After baseline measurements, subjects were randomly allocated to one of the three groups: control group (CON), exercise group (EX) or exercise associated to NMES (EX + NMES). All participants were evaluated at baseline (PRE) and at the end (POST) of the 8-week exercise program, by the same investigators. The study was performed between January 2019 and March 2020.

Sample size was estimated based on the effect sizes found for muscle strength variables after the inclusion of the first 4 patients in each group. According to these magnitudes, and assuming a significance level of 0.05 and power of 80%, the total sample size required to achieve statistical significance would be 9 participants per group.

2.2. Participants

The potential participants included 33 children previously diagnosed using a genetic test for CF and followed at the Children's Hospital Niño Jesus in Madrid. The inclusion criteria were patients with CF aged 6–17 years and living in the Madrid area (to be able to attend training sessions). Exclusion criteria were having severe lung deterioration, as defined by a forced expiratory volume in the first second (FEV_1) lower than 50% of the predicted, presenting with unstable clinical condition (i. e., hospitalization within the previous 3 months) and having a skeletal muscle disease or any other disorder impairing exercise practice. None of the patients included in the study were receiving CF modulator therapy.

2.3. Randomization

Participants were randomly assigned to either the CON, EX or EX + NMES groups using individual codes and the Excel randomize function. The researcher who performed data analysis and the physician responsible for clinical assessments were blinded to the participant randomization assignment. As this is an exercise-based intervention, it was not possible to blind researchers responsible for the training protocol. Participants and their parents or caregivers were explicitly informed to which group they were assigned, as well as to the study hypotheses, and told not to discuss their randomization assignment with other researchers or staff members.

2.4. Familiarization and reliability of outcome assessment

Before the start of the study, all participants underwent a familiarization period with all the tests for outcome assessment that are described below. The familiarization period included one session for treadmill testing and two sessions for functional/strength tests. Each session was preceded by a warm-up and ended with a cool-down of the same activities and duration used during the training period.

2.5. Exercise intervention and neuromuscular electrical stimulation

The exercise program was carried out for 8 weeks, 3 days per week (24 sessions in total), from Monday to Saturday. Resistance exercises were used and each session lasted for 60 min. The exercise plans were individualized to each patient. The training program started with a 15-min warm-up period, followed by a 35-min resistance training and a 10-min cool down period. The warm-up load was initially established at a heart rate corresponding to the ventilatory threshold (VT_1) measured at the beginning of the study using the cardiorespiratory exercise test (CPET). Subsequently, a circuit of the following six resistance exercises was performed: bench press, leg extension, leg press, leg curl, seated row and chest pull. In order to individualize training loads, the 5RM (maximum repetition) test was used, along with the subjective perception of effort (Borg scale). Once the maximum weight achieved in 5RM was obtained, the 1RM was estimated through the Bryzicki's formula [28], which allows setting the appropriate weights for each training stage. The test was carried out again at 4 weeks to individually adjust

training loads according to evolution. Initially, participants performed a set of 12–15 repetitions, ending in sets of 8–10 repetitions with a 60-s resting period between sets and 2-min between exercises. The load was gradually increased as each child's strength improved, that is, from 40 to 60% of the estimated 1RM at the start of the program to 70–80% of 1RM at the end of the program. All sessions were individually supervised by experienced professionals. The CON group was not submitted to any structured supervised exercise intervention. Patients followed the routine recommendations from the CF multidisciplinary team, which is a general recommendation to perform physical activities based on the WHO guidelines for children and adolescents.

NMES was applied to the quadriceps (vastus lateralis and medialis) and to the interscapular region (latissimus dorsi and trapezius), using the electrostimulator Myomed 632X (Enraf Nonius, Spain), simultaneously with the resistance exercises. Four surface electrodes (two 8×4 cm and two 4×4 cm) were used on each muscle group (quadriceps and interscapular). Each muscle group was stimulated simultaneously with a 250 ms pulse, 4 Hz frequency, and duration of 2 s on (concentric) and 4 s off (eccentric). The first exercise session was used to assess initial values for each child, since tolerance threshold is individualized. The intensity was progressively increased in the same session, and between different sessions, up to the maximum tolerance, without causing any significant discomfort or pain for the patient.

2.6. Outcomes

The primary outcome of the study was the changes in peripheral muscle strength. Secondary outcomes included changes in lung function, cardiorespiratory fitness, functional capacity and quality of life.

2.7. Assessments

2.7.1. Anthropometric data and body composition

Weight (kg) and height (cm) were measured with a mechanical scale (Asimed, Barys Plus C) and with a telescopic height gauge, respectively. The body mass index was also calculated (kg/m^2). All variables were expressed as absolute and z-score values.

2.7.2. Lung function

Spirometry was performed with a Master Screen spirometer (Jaeger, Germany) following the American Thoracic Society - European Respiratory Society (ATS/ERS) guideline [29]. The FEV$_1$, forced vital capacity (FVC), FEV$_1$/FVC ratio and the forced expiratory flow between 25 and 75% of the FVC (FEF$_{25–75\%}$) were evaluated. Data were expressed in absolute values and z-score based on the Global Lung Initiative (GLI) reference equation [30] establishing as a limit of normality (LIN) a z-score value for FEV$_1$ between −1.64 and + 1.64.

2.7.3. Cardiorespiratory fitness

In order to evaluate the cardiorespiratory fitness, a treadmill (Technogym Run Race 1400HC; Gambettola, Italy) maximum test was used. The protocol used began with an initial speed and inclination of 2.5 km.h^{-1} and 0.5%, respectively, with increases in both variables of 0.1 km.h^{-1} and 0.5%, respectively, every 15 s. Gas exchange data were measured breath-by-breath using open-circuit spirometry (Vmax 29C; SensorMedics; Yorba Linda, CA) and specific pediatric face masks along with electrocardiogram recording. The objective of the test was to determine the peak oxygen consumption (VO$_2$peak) and the VT$_1$ in response to a maximal effort. The VO$_2$peak was recorded as the highest value obtained for any continuous 20 s period [31]. The VT$_1$ was determined using the criteria of an increase in both the ventilatory equivalent for oxygen consumption (V$_E$/VO$_2$) and end-tidal pressure of

oxygen with no increase in the ventilatory equivalent for carbon dioxide production (V$_E$/VCO$_2$) [31]. The test was considered as maximum if the following criteria were met: (i) heart rate greater than 180 beats per minute; (ii) respiratory exchange ratio above 1.0 [32].

2.7.4. Functional tests (Agility walking and in stairs)

In order to measure children's functional mobility, we have used the Timed Up and Go (TUG) test of 10 m and the Timed Up and Down Stairs (TUDS) test. Both tests have been shown to be reliable and valid in healthy children and also in children with several diseases or disabilities [33,34]. The TUG test of 10 m is a measure of the time needed to stand up from a seated position in a chair, walk 10 m, turn around, return to the chair, and sit down. For the TUDS test, the time it took to ascend and descend 12 stairs was measured. All children used a hand railing in the TUDS test to diminish the risk of falling. Performance time in both tests was measured by the same investigator with the same stopwatch to the nearest 0.1 s.

2.7.5. Quality of life

The quality of life (QoL) was determined using the Spanish version (1.0) of the CF Questionnaire-Revised (CFQ-R) [35,36]. The ≤11-yr-old group completed the CFQ-R through an interview, whereas the 12- to 13-yr-old group completed the same CFQ-R themselves, and adolescents age ≥14-yr completed the CFQ-R version 14+. In addition, in children age ≤13-yr, a parent or caregiver completed the parent version of the CFQ-R. Response choices included ratings of frequency, likelihood, or difficulty on four-point scales of different domains, i.e., physical functioning, social functioning, emotional functioning, treatment burden, eating disturbances, body image, digestive symptoms, and respiratory symptoms. Individual scores were standardized on 0- to 100-point scales, with higher scores indicating better QoL, and we computed a total QoL score on the basis of the sum of the scores of each domain.

2.7.6. Muscle strength

Muscle strength was evaluated as described in Supplemental Fig. 1. After familiarization with the techniques of the movements involved (low paddle, pull ahead, chest press, leg press, knee extension and knee flexion lying down), tests were performed for the direct calculation of 5RM (maximum repetition). The test protocol consisted of performing 2 warm-up series at 50 and 70% of the perceived 5RM (15 and 10 minimum repetitions, respectively), with a resting period of 1 min between series. After 2 min of resting, a third series was performed using a load between 90 and 105% of 5RM, depending on the effort used in the last warm-up series. If the first attempt of 5RM was achieved, the resistance was increased by 2.5–5% and, after another 2-min resting, a new attempt was performed. If the first attempt of 5RM was not successful, the resistance was reduced by 2.5–5% and, after 2 min of rest, another attempt of 5RM was performed. The load was increased or decreased until the 5RM was achieved with a maximum of three attempts each 24 h (see Supplemental Fig. 1 for a detailed description) [37]. As the age of the population studied is wide, we have decided to normalize data by calculating the relative strength, that is, the weight achieved in each muscle group by the weight of the subject (both variables in kg). The equipment used to perform the tests was the STRIVE Pediatric resistance machines, USA.

2.8. Statistical analysis

Although all the results were analyzed by protocol and intention-to-treat analysis (ITT), only the ITT results are presented. The distribution and normality of the data were analyzed with the Shapiro-Wilk and Levene tests and with P-P and Q-Q plots. Data were expressed as mean

and standard deviation (mean ± SD) for parametric and as median and interquartile range for nonparametric variables. A one-way analysis of variance (ANOVA), chi-square (χ^2) test or Fisher's exact test, as appropriate, were used to compare differences between groups at baseline. A multivariate variance test of repeated measures (MANOVA) with two time and three group factors was used to assess the effects of training. In addition, in order to compare the effect of the experimental groups with control from PRE to POST, percent change was calculated as (POST - PRE)/PRE × 100. Differences between groups in percent change were assessed using a one-way ANOVA. Partial eta squared (η^2_p) was used as a measure of effect size. The level of statistical significance was set at $p < 0.05$. All statistical analysis was performed with SPSS 21.0 (IBM, Armonk, NY, USA).

3. Results

A total of 33 children and adolescents with CF were eligible for the study and were randomized equally to the three groups. However, six participants did not complete all measurements or discontinued the proposed intervention, resulting in a final sample of 11 patients for the control group and eight for each of the intervention groups (EX and EX + NMES). Fig. 1 shows the complete flow diagram of the study.

No significant differences were found at baseline between groups regarding demographic and anthropometric characteristics (Table 1).

Significant differences were found only for genotyping and the presence of *Burkholderia cepacia*. As for lung function, only the absolute values of FEV_1 and FVC were significantly different, although there were no differences in the normalized z-score values. Results indicated a sample of mild-to-moderate lung function impairment. The main baseline characteristics of the groups are presented in Table 1.

When cardiorespiratory fitness variables were evaluated, no significant interactions were found (group x time). A significant effect for time was demonstrated for V_E/VCO_2peak and test duration, as well as a significant effect for group and time was found for RERpeak (Table 2). Regarding functional capacity, both the TUG and TUDS test have shown significant group x time effects, indicating a better functional capacity in both EX and EX + NMES groups (Table 2). No significant changes between groups were seen for quality of life, both for the total score or the specific domains evaluated (data not shown).

Fig. 2 presents mean and standard deviation for muscle strength data. When the effects of exercise on peripheral muscle strength were evaluated, both intervention groups (EX and EX + NMES) presented large effect sizes and statistically significant differences, in percent change, when compared to the CON group, for the bench press ($p = 0.004$, $\eta^2_p = 0.401$), pectoral ($p = 0.001$, $\eta^2_p = 0.487$), dorsal ($p = 0.009$, $\eta^2_p = 0.333$) and handgrip ($p = 0.028$, $\eta^2_p = 0.278$) (Table 3). No significant differences were found between EX and EX + NMES groups.
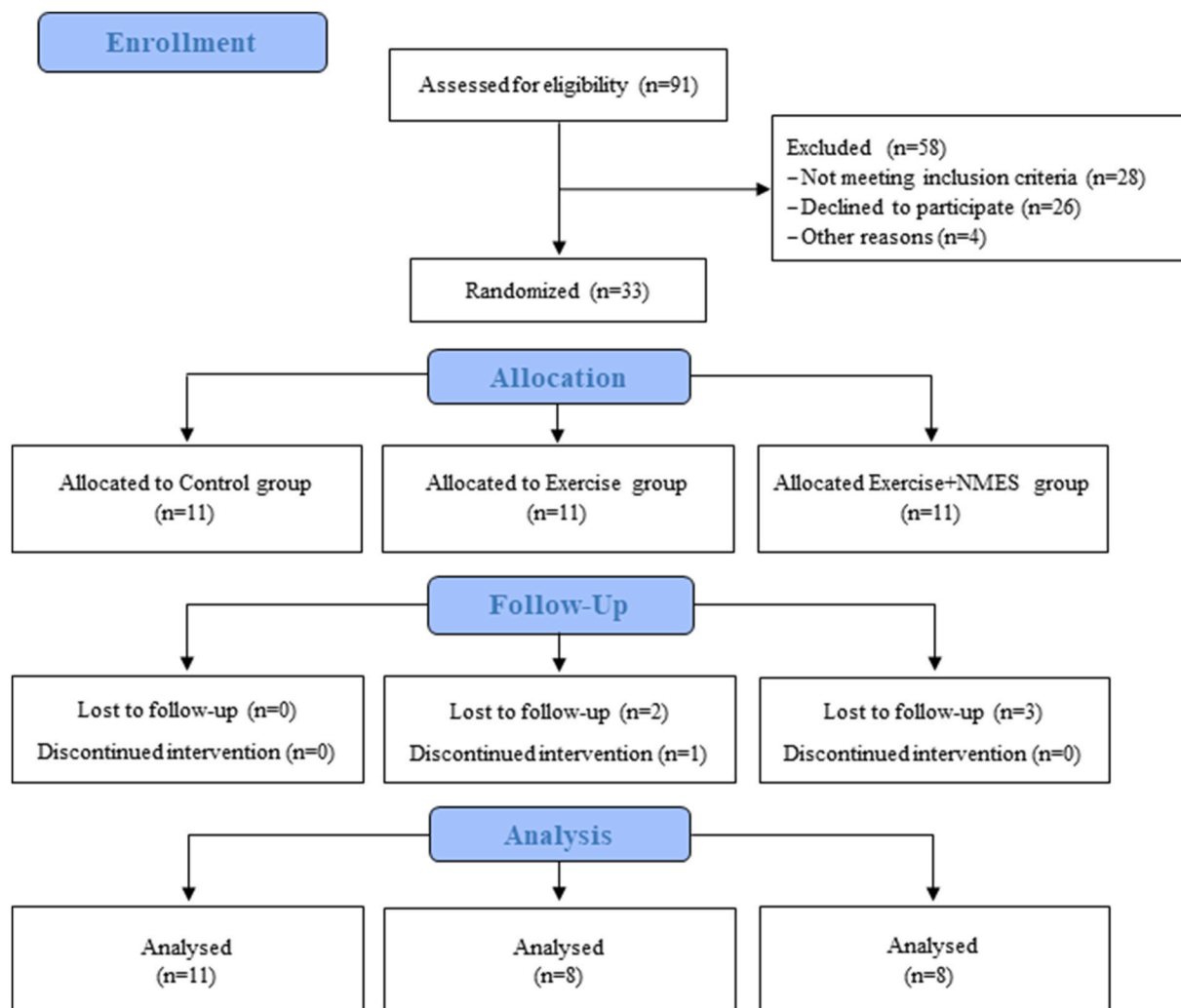

Fig. 1. Flow chart of the study.

Table 1

Characteristics of the study sample.

	CON (n = 11)	EX (n = 8)	EX + NMES (n = 8)	Total (n = 27)	*p*
Demographics					
Sex, Male, n (%)	8 (72.7)	5 (62.5)	6 (75.0)	19 (70.4)	0.840
Age (years), mean (SD)	11.7 (3.5)	12.8 (3.1)	13.8 (1.7)	12.6 (3.0)	0.347
Anthropometrics, mean (SD)					
Weight (kg)	34.4 (7.9)	44.1 (10.3)	45.3 (12.3)	40.5 (11.0)	0.051
Weight (z-score)	−1.04 (1.23)	−0.24 (1.18)	−0.56 (0.98)	−0.66 (1.16)	0.324
Height (cm)	143.5 (13.5)	152.3 (15.1)	157.2 (10.5)	150.1 (14.0)	0.090
Height (z-score)	−0.77 (1.15)	−0.27 (0.89)	−0.13 (0.69)	−0.43 (0.96)	0.324
BMI (kg/m^2)	16.4 (1.6)	18.8 (2.6)	18.0 (3.2)	17.6 (2.6)	0.106
BMI (z-score)	−0.83 (1.10)	−0.10 (1.34)	−0.66 (1.27)	−0.56 (1.22)	0.432
Genotyping, n (%)					
F508del homozygous	1 (9.1)	4 (50.0)	7 (87.5)	12 (44.4)	**0.002**
F508del heterozygous	9 (81.8)	2 (25.0)	0 (0)	11 (40.7)	
Others	1 (9.1)	2 (25.0)	1 (12.5)	4 (14.8)	
Lung Function, mean (SD)					
FEV$_1$ (L)	1.68 (0.32)	2.23 (0.73)	2.71 (0.96)	2.15 (0.79)	**0.012**
FEV$_1$ (z-score)	−1.98 (1.49)	−1.37 (1.63)	−0.91 (1.54)	−1.48 (1.56)	0.337
FVC (L)	2.13 (0.41)	2.87 (1.13)	3.33 (1.10)	2.71 (1.00)	**0.024**
FVC (z-score)	−1.47 (1.43)	−0.75 (1.68)	−0.48 (1.27)	−0.96 (1.48)	0.323
FEV$_1$/FVC	79.7 (10.7)	79.4 (9.5)	81.1 (8.5)	80.0 (9.4)	0.933
FEV$_1$/FVC (z-score)	−1.05 (1.32)	−1.09 (1.23)	−0.88 (1.00)	−1.01 (1.16)	0.934
Clinical diagnoses, n (%)					
Pancreatic insufficiency	10 (90.9)	7 (87.5)	8 (100)	25 (92.6)	0.610
Hepatic disease	2 (18.2)	1 (12.5)	0 (0)	3 (11.1)	0.456
Microbiologic data, n (%)					
Pseudomonas aeruginosa	8 (72.8)	6 (75.0)	6 (75.0)	20 (74.1)	0.408
Staphylococcus aureus sensible	10 (91.0)	6 (75)	8 (100)	24 (88.9)	0.139
Staphylococcus aureus resistant	2 (18.2)	3 (37.5)	1 (12.5)	6 (22.2)	0.716
Burkholderia cepacia	0 (0)	3 (37.5)	0 (0)	3 (11.1)	**0.018**
PAQ, mean (SD)	2.6 (0.7)	2.4 (0.8)	2.6 (0.5)	2.6 (0.6)	0.693
CFQ, mean (SD)	74.0 (9.1)	74.0 (6.6)	78.3 (10.1)	75.4 (8.7)	0.546

CON: control; EX: exercise; EX + NMES: exercise plus neuromuscular electrical stimulation; BMI: body mass index; FEV$_1$: forced expiratory volume in the first second; FVC: forced vital capacity; PAQ: Physical activity questionnaire; CFQ: cystic fibrosis quality of life questionnaire; L: liters; Kg: kilograms; SD: standard deviation. Differences between groups were calculated using One-way ANOVA, chi^2 test or exact test, as appropriate. Significance was set at 0.05.

4. Discussion

The results of the present study have shown that a supervised resistance-training program was able to increase muscle strength and functional capacity in children with CF. However, the addition of NMES did not increase the training effects found. These results are of importance to the rehabilitations of patients with CF, as muscle function has been demonstrated as a key factor for better clinical outcomes [7]. Moreover, no side effects of the resistance-training program or the use of NMES were found.

The general beneficial effects of anaerobic exercise programs have already been demonstrated for children with CF [38,39]. Although the possible extra benefits for physical health from a combination of aerobic and strength training are still not clear, the present study has demonstrated that a resistance exercise-training program increased peripheral muscle strength and functional performance, although no changes were seen for aerobic fitness. A previous study [40] in young adults with CF has shown that a strength program increased lung function and VO$_2$ similarly to the aerobic training. On the other hand, Orenstein et al. [38] have demonstrated that a strength training, for children with CF, had no positive effects on VO$_2$, with a significant decrease over time (12-month period). The complete scenario regarding the mechanisms between resistance-training and increased aerobic fitness is still not fully understood. To date, approximately 20 randomized controlled trials, with methodological quality from low-to-moderate, have been published to evaluate the effects of exercise on different parameters in patients with CF [21]. The evidence of the effects of both resistance and strength training or combined programs on exercise capacity, lung function and quality of life, is still very limited, which justifies the efforts to explore the role of muscular electrostimulation as an additional training tool. As for present results, we believe it is important to highlight that the sample included showed a high baseline VO$_2$peak ($\cong$ 41–45 mL kg^{-1}. min^{-1}), which is probably difficult to increase with any type of exercise program.

In spite of the absence of changes in aerobic fitness, the training program was able to increase functional capacity, as demonstrated by both the 10-m TUG and the TUDS test. Considering that both tests are of short duration and demand a predominantly anaerobic power [33,34], it is possible that the increased muscle strength induced in both exercise groups have played a role in the improvement seen for functional mobility. The data from present study also demonstrated a significant effect on peripheral muscle strength, including both upper and lower body muscle groups. Evidence on the topic suggests that muscle function has important clinical implications in CF [7] and may consist in a major determinant of exercise intolerance [12,13]. Although the differences between exercise programs may challenge the interpretation of findings, several training programs were able to increase muscle strength in patients with CF [21].

The use of NMES for children with neuromuscular diseases has been effective in improving physical function [24–26]. In addition, the skeletal muscle dysfunction and exercise intolerance are common in adults with severe chronic obstructive pulmonary disease (COPD) and the use of NMES is effective in the treatment of patients who cannot participate in conventional pulmonary rehabilitation [41]. Evidence suggests that the use of NMES in people with COPD, either alone or in conjunction with conventional physical training, improve the function of peripheral muscles, increase exercise capacity and functional performance, reduce symptoms and improve health-related quality of life. Further, in patients

Table 2

Effects of exercise and exercise with neuromuscular electrical stimulation on cardiorespiratory fitness and functional capacity.

Variables	Group	Pre	Post	*p-value* group	*p-value* time	*p-value* group x time
Cardiorespiratory fitness						
HRbaseline (bpm)	**CON**	104.0 ± 12,4	99.6 ± 13.8			
	EX	101.1 ± 7.2	97.3 ± 6.0	0.594	0.303	0.854
	EX + NMES	104.4 ± 14.5	103.6 ± 13.2			
VO_2VT_1 (mL.Kg^{-1}.min^{-1})	**CON**	30.3 ± 4.7	25.8 ± 4.2			
	EX	26.6 ± 2.4	24.3 ± 2.6	0.300	0.082	0.185
	EX + NMES	25.7 ± 6.4	26.4 ± 5.3			
VO_2VT_1 (%VO$_2$peak)	**CON**	71.8 ± 12.3	62.1 ± 11.6			
	EX	65.2 ± 10.9	61.7 ± 9.6	0.083	0.074	0.365
	EX + NMES	57.8 ± 11.1	56.7 ± 7.1			
HRpeak (bpm)	**CON**	182.6 ± 13.1	184.1 ± 9.8			
	EX	185.0 ± 7.7	176.8 ± 7.9	0.764	0.737	0.064
	EX + NMES	180.1 ± 4.4	184.6 ± 5.8			
$V_E$peak (L.min^{-1})	**CON**	54.7 ± 15.7	54.1 ± 15.5			
	EXE	66.2 ± 26.7	61.0 ± 23.2	0.552	0.661	0.110
	EXE + NMES	59.5 ± 26.3	68.9 ± 21.7			
VO$_2$peak (mL.Kg^{-1}.min^{-1})	**CON**	42.7 ± 6.1	42.4 ± 7.3			
	EX	41.7 ± 8.1	40.1 ± 6.5	0.373	0.877	0.583
	EX + NMES	45.3 ± 10.3	46.6 ± 7.5			
V_E/VO$_2$peak	**CON**	34.9 ± 2.8	35.3 ± 4.8			
	EX	34.6 ± 4.7	34.8 ± 5.2	0.142	0.113	0.191
	EX + NMES	29.0 ± 6.2	33.1 ± 5.7			
V_E/VCO$_2$peak	**CON**	29.6 ± 4.1	32.1 ± 5.8			
	EX	33.9 ± 5.7	35.3 ± 6.7	0.295	**0.011**	0.312
	EX + NMES	29.4 ± 4.3	35.1 ± 6.6			
RERpeak	**CON**	1.25 ± 0.20	1.15 ± 0.12			
	EX	1.18 ± 0.19	1.03 ± 0.10	**0.005**	**0.019**	0.266
	EX + NMES	1.00 ± 0.11	1.00 ± 0.05			
Duration (minutes)	**CON**	10.3 ± 2.3	10.5 ± 2.0			
	EX	10.8 ± 1.3	11.3 ± 1.9	0.617	**0.045**	0.248
	EX + NMES	10.3 ± 2.0	12.1 ± 2.1			
Functional Capacity						
TUDS (seconds)	**CON**	5.9 ± 1.3	6.0 ± 1.1			
	EX	6.3 ± 0.4	5.8 ± 0.8	0.340	**0.009**	**0.030**
	EX + NMES	5.8 ± 1.1	5.0 ± 0.7			
TUG (seconds)	**CON**	9.9 ± 1.3	9.8 ± 1.1			
	EX	9.7 ± 0.8	9.1 ± 0.9	0.497	**0.001**	**0.020**
	EX + NMES	10.0 ± 1.5	8,6 ± 0.8			

CON: control; EX: exercise; EX + NMES: exercise plus neuromuscular electrical stimulation; VO$_2$: oxygen consumption; HR: heart rate; V_E: minute ventilation; VT$_1$: ventilatory threshold; V_E/VO$_2$: ventilatory equivalent for oxygen consumption; V_E/VCO$_2$: ventilatory equivalent for carbon dioxide production; L: liters; Kg: kilograms; bpm: beats per minute; TUG: timed up and go; TUDS: timed up and down stairs. Differences between group, time and group × time interaction were evaluated using two-way repeated measure ANOVA. Significance was set at 0.05.

who were the most debilitated, the addition of NMES to exercise training has accelerated the functional performance recovery [42]. Although evidence for its use in CF is very limited, a previous study [22] in severely compromised adults has shown positive results for peripheral muscle strength, body weight, quality of life and ventilation requirements during exercise. To the best of our knowledge, our study is the first to evaluate the use of NMES in children with mild-to-moderate CF disease. Our results have shown no additional benefits of adding NMES to the exercise-training program used. The absence of benefits may be related to the good physical fitness of the sample, with no signs of peripheral muscle dysfunction. Once confirmed, the results indicate that NMES may have a role to be used particularly to severe patients with CF, where muscle abnormalities are more evident.

The evidence regarding an increase in lung function after an exercise program is still inconclusive, as there is data showing both an improvement [40] or no changes [39]. The present results have shown that an 8-week resistance-training program did not significantly change lung function parameters in children with CF. Similarly, we found no significant improvements in quality of life, which has also been previously demonstrated [39,43].

The present study has also limitations, including the difference in genotyping between groups. Although there is evidence to support that its effect on exercise variables is not substantial, it may have influenced present results. In addition, the mild-to-moderate impairment of the sample could also affect results, as smaller effects are expected in patients with a high aerobic fitness and lower muscular abnormalities.

5. Conclusions

The results indicate that an 8-week supervised resistance exercise-training program led to improvements in muscle strength and functional capacity in CF patients with mild-to-moderate pulmonary impairment. The addition of NMES to the training program resulted in no extra favorable effects. These results highlight the benefits of the resistance training for children with CF. Further studies may evaluate the use of NMES for CF patients with moderate-to-severe peripheral
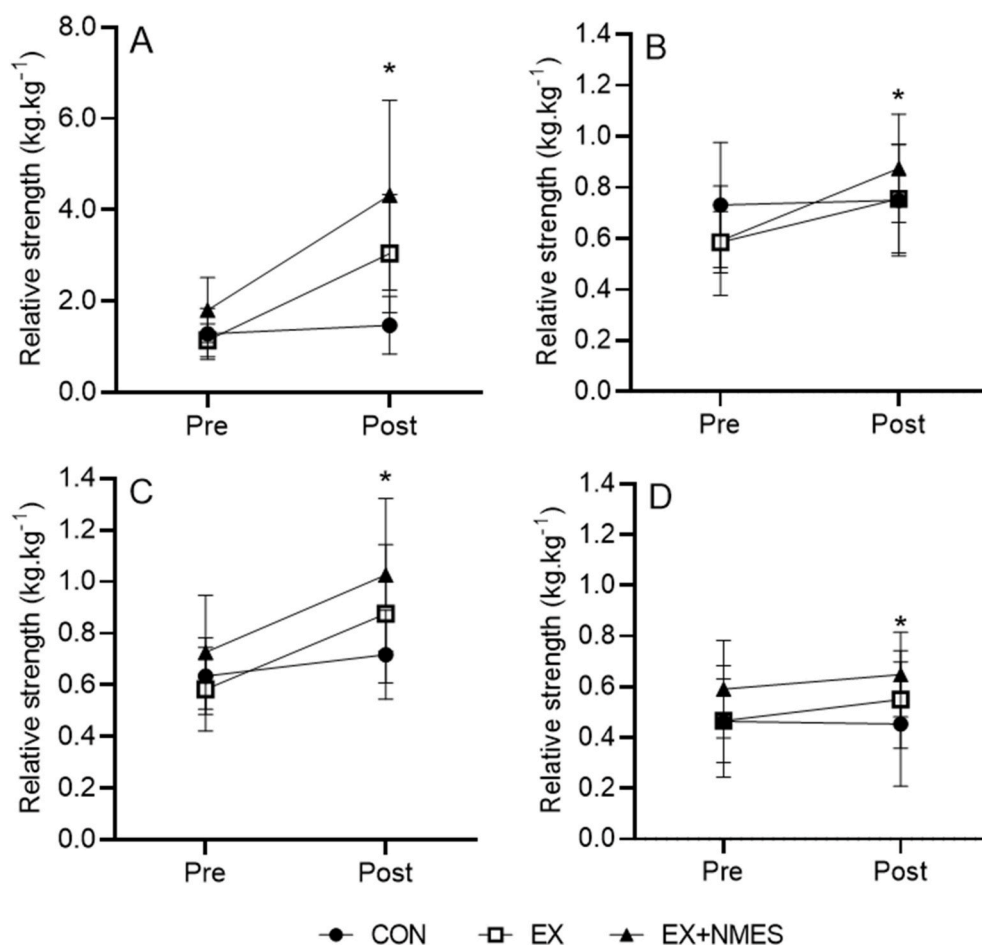
Fig. 2. Effects of exercise-training and exercise plus neuromuscular electrical stimulation on peripheral muscle strength in children with cystic fibrosis. (A) Bench press; (B) Pectoral; (C) Dorsal; (D) Handgrip. Kg: kilogram; CON: control group; EX: exercise group; EX + NMES: exercise + neuromuscular electrical stimulation. Data presented as mean and standard deviation. Differences were analyzed using a two-way analysis of variance (ANOVA) with repeated measures. *indicates significant differences for group × time interaction ($p <$ 0.05).

Table 3
Between-group comparisons in percent change from pre to post for muscle strength variables.

	CON (n = 9)	EX (n = 8)	EX + NMES (n = 8)	Total (n = 25)	p	η^2_p
Muscle strength, mean (SD)						
Bench press	21.9 (39.8)	167.7 (82.3)	151.8 (122.6)	110.1 (107.2)	**0.004**	0.401
Pectoral	5.8 (18.7)	28.1 (17.4)	56.0 (30.1)	29.0 (30.2)	**0.001**	0.487
Dorsal	4.6 (37.6)	52.1 (28.8)	44.3 (27.7)	31.4 (37.8)	**0.009**	0.333
Handgrip	−4.4 (10.8)	21.2 (27.4)	12.1 (13.6)	9.0 (20.8)	**0.028**	0.278

SD: standard deviation; CON: control; EX: exercise; EX + NMES: exercise plus neuromuscular electrical stimulation. Differences were assessed using One-way ANOVA. Significance level was set at 0.05. Standardized effect sizes were reported using Partial Eta Squared (η^2_p).

muscle function abnormalities.

CRediT authorship contribution statement

Márcio Vinícius Fagundes Donadio: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Fernando Cobo-Vicente:** Data curation, Methodology, Investigation, Writing – review & editing. **Alejandro F. San Juan:** Investigation, Methodology, Writing – review & editing. **Verónica Sanz-Santiago:** Investigation, Writing – review & editing. **Álvaro Fernández-Luna:** Investigation, Methodology, Writing – review & editing. **Tamara Iturriaga Ramirez:** Data curation, Methodology, Investigation, Writing – review & editing. **José Ramón Villa Asensi:** Supervision, Writing – review & editing. **Margarita Pérez-Ruiz:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.106798.

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