Effects of combined endurance and resistance training in Amyotrophic Lateral Sclerosis: A pilot, randomized, controlled study

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Abstract

Based on available evidence, muscle strengthening and cardiovascular exercises can help maintain function and not adversely affect the progression of disease in patients with ALS. However, this evidence is not sufficiently detailed to recommend a specific exercise prescription. The purpose of this project was to assess clinical outcomes of a combined exercise programme to increase knowledge of rehabilitation in ALS patients. 38 ALS patients were assigned randomly to two groups: one group underwent a specific exercise programme (ALS-EP) based on a moderate aerobic workout and isometric contractions, and the second group followed a standard neuromotor rehabilitation treatment. Objective evaluation consisted of cardiovascular measures, muscle strength and fatigue. Some positive effects of physical activity on ALS patients were found. Among the benefits, an overall improvement of functional independence in all patients, independently of the type of exercise conducted was seen. In addition, improvements in muscle power, oxygen consumption and fatigue were specifically observed in the ALS-EP group, all hallmarks of a training effect for the specific exercises. In conclusion, moderate intensity exercise is beneficial in ALS, helping in avoiding deconditioning and muscle atrophy resulting from progressive inactivity.

Key Words: Amyotrophic Lateral Sclerosis, neurorehabilitation, endurance training, isometric exercise

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Motor neuron diseases (MND) include a heterogeneous spectrum of inherited and sporadic clinical disorders of the upper motor neurons (UMN), lower motor neurons (LMN) or a combination of both. MND are characterized by progressive degeneration and loss of motor neurons in the spinal cord, brain stem, or motor cortex, and manifest clinically as muscle weakness, atrophy, and corticospinal tract signs and symptoms in various combinations.[1] Differently from most of neuromuscular pathologies, where a moderate consistent exercise is recommended, physical activity in ALS is still much debated. In the past, patients were frequently suggested to avoid regular exercise in order to preserve muscle strength.[2] In a recent study, it has been demonstrated that resistance and endurance exercise are safe to be performed without any worsening of outcomes in ALS patients.[3] However, inactivity can involve cardiovascular deconditioning and atrophy from disuse that further superimpose the weakness caused by the ALS disease itself.[3] If the reduced level of motor activity persists, ALS patients can develop severe deconditioning, muscle atrophy and tendon retractions that cause contractures, pain and higher difficulty in performing daily activities. Current clinical management for people with ALS is primarily individualized rehabilitation that may or may not include strengthening or aerobic exercise prescription. The continued lack of robust evidence regarding the efficacy and benefits of exercise in people with ALS may influence the availability, accessibility and quality of rehabilitation services provided for this group. Exercise, when prescribed appropriately, may be physically and psychologically important for people with ALS, especially in the earlier stages of the disease. Currently, rehabilitation of ALS patients is primarily individualized and sometimes may include strengthening and aerobic exercise.[4] However, the lack of evidence of impact and

efficacy of exercise in maintaining motor neuron integrity, motor function, and survival in ALS influences the availability, accessibility and quality of treatments.[4] Previous animal studies had provided good basic scientific information about the effects of endurance exercise training at moderate intensity showing a higher survival and a reduction of motor neuron degeneration in mice with SOD-1-induced ALS.[5,6] Recent SOD-1 ALS mice study, have proposed molecular basis for the differential effects of specific exercise type and intensity in ALS; in particularly, the switching to glycolytic muscle metabolism and the activation of the fast motor unit induced by well-designed exercise programs (swimming), may provide synergistic beneficial effects for ALS patients.[7,8] Considering that, in animal studies the neurons controlling fast fibers were noted to degenerate early in the course of ALS, other authors advise to minimize stress on fast twitch muscle fibers.[9,10] However, in humans, findings are more heterogeneous. In humans, an association between physical activity and ALS was postulated by some studies; recently a European Population-Based Case–Control.[11] Study concluded that physical activity is not a risk and may eventually be protective against the disease. Another review concluded that current evidence for physical activity as a risk factor in MND is limited.[12] Several authors have attempted to assess functional improvements after moderate exercise highlighting short-term benefits in producing a slower rate of decline in terms of endurance, spasticity and motor deterioration, but not in muscle strength.[4,10,13-15] On the other hand, other studies lay out some concerns on the exercise programme that should consider the underlying pathophysiology of ALS, avoiding high-intensity exercise that can stress the fast-twitch muscle fibers and being focused on reduction of spasticity, strengthening of weak muscles, and minimization of fatigue.[10] Overall, aerobic exercises, early and at mild to moderate intensities, seem to be beneficial in muscle strengthening and cardiovascular exercise can help maintain function, prevent further deconditioning and atrophy and not adversely affect the progression of the disease.[3-10]

Table 1. *Baseline characteristics of exercise programme group (ALS-EP) and standard neuromotor rehabilitation treatment group (ALS-SNT). ALSFS-R, Amyotrophic Lateral Sclerosis Functional Scale- revised; FIM, Functional Independence Measure; FSS, Fatigue Severity Scale; MRC sum score, Medical Research Concil sum score.*

	ALS-EP n=23 mean±SD	**ALS-SNT n=15** mean±SD
Age, yr	61.6 ± 10.6	59.8 ± 14.7
Gender, F/M	10/13	4/10
Onset,Spinal/Bulbar	22/1	15/0
Disease duration, mo	30.2±11.8	30.3±6.7
ALSFRS-R	36.1±4.71	34.5±3.6
ALSFRS-R, Bulbar subscore	9.89±1.7	9.73±1.7
Rate of progression	0.4±0.18	0.4±0.05
FIM	79.73±6.1	78.0±8.3
FSS	5.4±0.27	5.4±0.2
Resting heart rate, bpm	80.52±5.4	78.80±8.47
Oxygen Consumption, ml/min/kg	15.36±2.0	12.67±1.60
Ventilation, L/min	25.95±5.2	24.49±5.62
MRC Sum Score	40.26±2.45	39.87±4.24
Right Biceps Muscle, kg/min	66.96±24.95	73.13±16.99
Left Biceps Muscle, kg/min	70.65±19.53	80.27±14.60
Right Tibial Muscle, kg/min	77.11±34.92	57.93±27.74
Left Tibial Muscle, kg/min	77.21±36.11	60.80±32.30
Six Minute Walk Test, mt	265.17±81.37	236.26±76.26

Table 2. *The cardiovascular and metabolic data of ALS-EP patients; I (initial), F (final); HR 65% (heart rate corresponded to 65% for aerobic training); RHR (Resting heart rate bpm); VO2 (Oxygen Consumption, ml/min/kg); 6 MW (Six Minute Walk Test, mt); MRCss (MRC Sum Score)*

ALS-EP	age	HR 65%	RHR I	RHR F	VO_2 I	VO_2 F	6MW I	6MW F	MRCss I	MRCSs F
1	71	95	88	81	13	8,1	152,5	170,5	42	52
2	54	110	83	78	18,1	15,4	392	530	38	50
3	65	100	89	82	14,1	9	294,5	298,75	41	49
4	72	95	85	79	12,9	12,2	316	458	42	48
5	53	110	81	77	16,4	8,6	48	68	41	49
6	71	95	78	73	15,4	9,5	216	267	36	41
7	65	100	72	68	17,3	11,4	256	320,5	34	42
8	68	100	74	67	12,8	9,3	315	395	40	48
9	64	100	78	71	15,6	11,5	375	400	40	50
10	59	105	84	78	16,7	13,8	340	557	38	42
11	73	95	88	81	15,9	13,1	325	455	41	52
12	63	100	83	78	17,5	12,5	238	280	38	47
13	26	125	89	82	17,8	13,6	275	340	42	49
14	67	100	85	79	18,3	14,3	245	325	45	52
15	62	105	81	77	19,5	14,4	135	225	41	48
16	49	110	78	73	14,6	10,1	305	405	42	49
17	57	100	72	68	15,2	13,1	225	275	41	48
18	60	105	74	67	13,4	11,4	325	375	42	49
19	61	105	78	71	13,2	9,1	225	275	38	45
20	74	95	84	78	14,6	8	260	325	42	49
21	63	105	77	73	14	11,2	325	350	38	46
22	71	95	76	69	13,2	7,9	325	440	42	50
23	50	110	75	71	13,7	8,9	186	210	42	51

However, this evidence is not sufficiently detailed to recommend a specific treatment and there is complete lack of randomised clinical trials examining aerobic training in ALS patients. The present study was aimed at evaluating the effect of a moderate exercise programme based on aerobic training and isometric sub-maximal contractions of muscles, on changes in muscle strength, fatigue and cardiovascular parameters. This programme was designed to strengthen the weak muscles, facilitate musculoskeletal resistance and minimize fatigue to prevent deconditioning and atrophy not directly caused by the disease.

Materials and Methods

Participants

Forty-six patients admitted to the Foundation San Camillo Hospital for rehabilitation were consecutively enrolled in this study. All patients fulfilled the revised El Escorial criteria for clinically probable, laboratory-supported probable, or definite ALS.[20] Inclusion criteria included: sporadic or familial ALS; mild to moderate disabilities assessed by Sinaki-Mulder stages I-II-III.[19] Exclusion criteria were as follows: history of other neurological diseases, lost ability to walk (any assistive device was allowed), mechanical ventilation, heart or respiratory failure, metabolic disorders, any severe active neuropsychological illness making a patient unable to understand and perform the instructions. All patients included in our study were taking riluzole. None carried the SOD1 mutation. Before being enrolled in the study, an evaluation of oxygen consumption was carried out. No participants reported dyspnoea or respiratory insufficiency as assessed by forced vital capacity and nocturnal oximetry. Patients were assigned randomly to two groups: one group (26 patients, 9 females, mean age 61.6±10) underwent a specific exercise programme (ALS-EP) and the second group (20 patients, 8 females, mean age 59.2±14) followed the standard neuromotor

rehabilitation treatment (ALS-SNR). Both groups had no significant difference in their age, gender, time from disease onset, percentage of bulbar onset, rate of progression and disability at time of inclusion in the study (Table 1). The rate of progression of ALS was calculated by dividing the ALSFRS-R total score by symptom duration (months) and seems to represent an independent and robust prognostic biomarker for ALS.[21] Functional disability was assessed by the revised ALS Functional Rating Scale (ALSFRS-r) and the bulbar involvement was scored using the part of the ALSFRS-r assessing speech, salivation and swallowing. The experimental procedure was approved by the local Ethics Committee for medical research, and all participants gave informed written consent.

Exercise Protocol

The exercise protocol has been set based on the recommendations of the American College of Sports Medicine (ACSM).[22] The specific exercise programme consisted of a series of exercises that included an individualized progressive training of muscular strengthening and aerobic endurance, under the supervision of two experienced physical therapists. To be sure to avoid muscle damage, we have chosen the submaximal isometric contraction to strengthen the weak muscles with a score of 3, 4- or 4 as measured by the Medical Research Council scale (MRC). The repetitions were 3 for each bilateral muscle segment and were performed for a time interval, determined by calculating 80% of the time of maximum contraction; each repetition was separated by 30 seconds of rest. The exercise was carried out using rubber bands with a sequential system of progressive resistance and followed by stretching. The use of elastic bands reduces the risk of orthopedic and muscular injuries. The series of exercises was performed daily for 5 weeks. Aerobic exercise was performed to a sub-maximal intensity of 65% of maximum heart rate adjusted for age, with a duration of 15-20 minutes (in Tables 2a-2b the HR corresponding to 65% are summarized for each patient). Based on the weakness pattern and the level of disability of each patient, we chose to use a cycle ergometer, ergometry arm-leg and/or treadmill. Exercises were carried out with continuous monitoring of heart rate and saturimetry. The series of exercises was performed daily for 5 weeks, and overall each exercise session lasted about one hour. The second group of patients (ALS-SNR) followed a 5-week programme of standard neurorehabilitation, consisting of one-hour sessions of stretching, active mobilization and general muscle reinforcement; this last treatment has been set within the limits of patient reported fatigue and avoiding eccentric and concentric contractions. Furthermore, all patients underwent speech, occupational and psychological therapies, based on individual clinical and functional profiles.

Clinical assessment

All patients were assessed at the beginning and at the end of treatment by two evaluators with experience in neurorehabilitation, blinded to the treatment patients received. Functional autonomy was assessed by the

Table 3. *The cardiovascular and metabolic data of ALS-SNP patients*

ALS-SNT	age	HR 65%	RHR I	RHR F	VO_2 I	VO_2 F	6MW I	6MW F	MRCss I	MRCSs F
1	54	110	87	85	13	22,4	157,5	158,5	43	46
2	65	100	91	88	13,5	21	157,5	158,9	42	45
3	57	110	83	79	13,9	19,3	172,3	172	38	41
4	58	105	86	84	10,4	38	242	242	48	51
5	57	110	85	81	12,4	21	158	157,5	42	45
6	33	120	81	80	9,4	23,7	250	250	41	43
7	60	105	82	80	12	24	335	337	39	40
8	63	95	56	70	15	30	150	170	38	39
9	29	125	72	75	15,1	30,2	305	307	44	45
10	45	115	81	78	18	26,6	280	290	38	38
11	76	95	78	79	11,9	17	168	167	36	36
12	79	90	72	71	11	28,2	188	188	36	36
13	73	95	78	79	12,8	26,7	275	280	40	41
14	75	95	78	76	9,9	17	270	271	36	36
15	64	100	72	69	12,6	22,3	395	398	38	38

Functional Independence Measure (FIM). The six-minute walk test (6MWT) was used to identify gait speed thresholds supporting functional ambulation and the effects of fatigue on patients' walking capacity. Muscle strength was evaluated by the MRC Muscle Grading Scale and a dynamometer able to quantify muscle strength reliably (CIT Technics BV, Groningen, the Netherlands), with a reset button and a curved applicator. The muscular strength was assessed by the mean value of three consecutive muscular contractions of Deltoid, Biceps, Wrist extensor, Ileopsoas, Quadriceps femoris, Tibialis anterior. Positions of patient and instrument were standardized as described by Van der Ploeg et al.[23] The total MRC sum score (MRCSS), ranging from 0 (total paralysis) to 60 (normal strength), was calculated by the sum of the MRC score of the 6 muscles on both sides, each muscle graded from 0 to 5. Gas analysis was undertaken using the ergometer metabolic system Fitmate (Cosmed©, Rome, Italy) (24-25) following a 5-min warm-up at 30-W cycling and a pedalling cadence up to achieve 65% of the predicted maximum heart rate (HRmax) for 10 minutes. The HRmax was predicted from 220 beats min - age. Speed, resting heart rate and during exercise, ventilation and oxygen uptake were monitored, and the linear regression relating to HR and the volume of O2 (VO2) at submaximal work was extrapolated. Sub maximal oxygen consumption (VO2submax) was measured by Fitmate, using the following formula: VO2submax (ml/min/kg) = (HR × SV) × [a-vO2], where SV is stroke volume, and a-v O2 is arteriovenous oxygen difference in the oxygen content of the blood between the arterial blood and the venous blood. VO2submax was measured at the same load of exercise before the aerobic training and at the end of the study. Finally, the Fatigue Severity Scale (FSS) was administered to know the degree of fatigue and its effect on the activities of the patients. All patients performed a creatine kinase (CK) test to evaluate potential muscle damage as a consequence of level and intensity of physical exercise. No patients showed altered CK values before and after treatment.

Statistical analysis

To test for a statistically significant effect of exercise over the treatment period and whether this effect changed in relation to type of treatment, a mixed model, with group (exercise vs. control) and time (T0 vs. T1) as factors, was applied to the FSS and FIM scales, the cardio-respiratory and muscular measurements.[26,27] Model assumptions were verified through analysis of residuals. In case of heterogeneity, a variance covariate structure was introduced into the model and data were transformed with Box-Cox method in case of evidence of non-normality. Homogeneity of the two groups at T0 was assessed in relation to the ALSFRSr scale, duration of disease, progression rate and age using either the t-test or the non-parametric Mann-Witney test according to whether the data were found Gaussian or not. Correlation between outcome measures was tested with either Pearson or non-parametric Kendall test. Bonferroni correction was then used.[28] A Shapiro-Wilk test was performed to test for normality of the data. Data were tested at 95% significance level.

Table 4. *Functional and cardiopulmonary changes after training.*

	ALS-EP n=23 mean±SD	**ALS-SNT n=15** mean±SD
FIM	4.56±1.16*°	1.8±1.37*
FSS	1.29±0.21*	-0.21±0.16
Resting heart rate, bpm	-5.7±1.29	-0.53±4.47
Oxygen Consumption, ml/min/kg	-4.16±1.71*°	0.10±1.53
Ventilation, L/min	-3.59±4.73	0.34±4.64
MRC Sum Score	7.83±1.80*°	1.53±1.13
Right Biceps, kg/min	9.26±13.17*°	-0.73±1.10
Left Biceps, kg/min	8.1810.09±	-0.54±1.35
Right Tibial, kg/min	9.28±12.96	-0.13±1.46
Left Tibial, kg/min	8.44±17.27	-1.00±1.41
Six Minute Walk Test, mt	71.56±50.72	2.90±5.48

* Significant effect of time, $p<0.05$; ° Significant difference between groups, $p<0.05$

Results

At T0, both groups had the same degree of disability evaluated by the ALS-FRSr scale (p=0.27). Five bulbar onset patients were in the ALS-SNR group and one was in the ALS-EP group. Eight patients dropped out and 38 completed the study: the remaining patients were 23 attributable to the group of the specific exercise protocol and 15 to the group of standard rehabilitation. The cardiovascular and metabolic data of ALS-EP and ALS-SNP groups are summarized in Table 3. Significant differences in clinical and functional assessment are summarized in Table 4. The FIM scale was found correlated with Ventilation during exercise (r=0.25,p<0.01), resting HR (r=- 0.20,p=0.01), Right Biceps strength (r=0.24; p<0.01) and the six-minute walk test measurements (r=0.23,p<0.01). The FSS scale correlated with the Oxygen Consumption (r=0.26,p<0.01), resting HR (r=0.29,p<0.01), Right Biceps and Tibial strength (r=- 0.21,p=0.01,r=-0.19,p=0.02, respectively), the MRC Sum Score (r=-0.28,p<0.01) and the Six Minute walk test (r=-0.27,p<0.01).

Discussion

The positive effects of exercise in healthy people are, in general, well documented and have been largely demonstrated. Accordingly, physical inactivity is associated with increasing risk of many adverse health conditions.[29] This is more relevant in the process of aging or some neuromuscular disorders where a progressive degradation of the neuromuscular system manifests by a steady decline in muscle mass and strength. In fact, at the level of the single motor unit, aging and disease can be associated with muscle atrophy. Furthermore, recent data show that physical activity promotes reinnervation of muscle fibers in aging.[30-35] In ALS, conflicting results have weakened the role of physical exercise, though a growing number of data indicates the safe and the beneficial effects of physical activity.[3,36,37] Among the benefits, we found an overall improvement of the score on functional independence scale in all patients, independently of the type of exercise conducted (specific programme or standard neuromotor rehabilitation treatment). In addition, improvements in muscle power (expressed by the MRC scale), oxygen consumption (measured by VO2submax) and fatigue were specifically observed in the EP group, all hallmarks of a training effect for the specific exercise programme. As for physical activity in general, improvements can potentially reduce the strains of daily living by increasing reserve capacities.[38] This would allow ALS patients to meet the physiological demands required for activities of daily living more effectively, reflecting an increase of their score on functional independence scale. Examining our combined exercise programme, our purpose was to assess the clinical efficacy of a programme of moderate aerobic and isometric exercises, through an objective assessment of muscle strength, fatigue and cardiovascular parameters, in the early stage of ALS. The specific exercise programme was based on a standardized training consisting of an aerobic workout of moderate entity and muscle contractions. As for the aerobic exercise, treadmill or cycloergometer training is a highly repetitive form of gait training that promotes specific practice and can provide an aerobic training stimulus. Aerobic training can however primarily increase aerobic capacity through cardiorespiratory reconditioning and promote cardiovascular function, improving cardiovagal modulation. Although there are no data on ALS patients, it has been shown that an increase in neuromuscular activity (e.g. repeated exercise), results in a fast-to-slow transition, and that the lack of activity (e.g. resulting from denervation), induces a slow-to-fast transition.[8] These considerations suggest that aerobic exercise might be the best option for exercise prescription. In parallel to aerobic training, resistance exercises were set accurately, defining the type of contraction, the muscle segments to be reinforced, and the number of repetitions per session. In our study, a submaximal isometric contraction was chosen to avoid muscle damage from mechanical and bioelectrical overload, or metabolic stress, especially to the fast twitch fatigable muscular fibers. During isometric exercise, in fact, the muscle is activated, maintaining a constant length, and reaches a state of maximum tension safely. Recent studies have also shown that isometric exercises can maximize motor unit activity in terms of increase of the firing rates of active motor units and recruitment of other motor units that usually are inactive.[39] This mechanism can be crucial in strengthening a denervated muscle and could explain the improvement of MRC muscle scale that we observed in our patients after the five-week training programme. In summary, the use of a combined protocol of aerobic and resistance training (below maximal effort) seems to have positive effects in terms of energy and fatigue required to perform activities of daily living, and is associated with increased function and independence. A lower requirement for oxygen by the working muscle during submaximal tasks indicates better walking economy. However, the significant increase in muscular strength expressed by the MRCSS not supported by a change of dynamometric measures of the examined muscles could indicate that the submaximal isometric contractions used were too mild and precautionary. Aerobic training can however primarily increase aerobic capacity through cardiorespiratory reconditioning and promote cardiovascular function, improving cardiovagal modulation. Although there are no data on ALS patients, it has been shown that an increase in neuromuscular activity (e.g. repeated exercise), results in a fast-to-slow transition, and that the lack of activity (e.g. resulting from denervation), induces a slow-to-fast transition.[8] These considerations suggest that aerobic exercise might be the best option for exercise prescription. In parallel to aerobic training, resistance exercises were set accurately, defining the type of contraction, the muscle segments to

be reinforced, and the number of repetitions per session. In our study, a submaximal isometric contraction was chosen to avoid muscle damage from mechanical and bioelectrical overload, or metabolic stress, especially to the fast twitch fatigable muscular fibers. During isometric exercise, in fact, the muscle is activated, maintaining a constant length, and reaches a state of maximum tension safely. Recent studies have also shown that isometric exercises can maximize motor unit activity in terms of increase of the firing rates of active motor units and recruitment of other motor units that usually are inactive.[40] This mechanism can be crucial in strengthening a denervated muscle and could explain the improvement of MRC muscle scale that we observed in our patients after the five-week training programme. In summary, the use of a combined protocol of aerobic and resistance training (well below maximal effort) seems to have positive effects in terms of energy and fatigue required to perform activities of daily living, and is associated with increased function and independence. A lower requirement for oxygen by the working muscle during submaximal tasks indicates better walking economy. However, the significant increase in muscular strength expressed by the MRCSS not supported by a change of dynamometric measures of the examined muscles could indicate that the submaximal isometric contractions used were too mild and precautionary. suggest that specific rehabilitation programs can counter out the progressive motor deficit of ALS. We believe that moderate exercise can be a reasonable recommendation to establish specific exercise therapy and to improve clinical practice in ALS Centers. Integration with bio molecular data and/or biopsy and a longer exercise programme would be useful to evaluate the effect of exercise on motoneuron efficiency, evidencing cellular and metabolic changes and to verify the effect of rehabilitative intervention on the natural history of the disease.

List of acronyms

ALS - Amyotrophic Lateral Sclerosis
ALS-EP - specific exercise programme
LMN - lower motor neurons
MND - motor neuron diseases
UMN - upper motor neurons
ALSFS-r - Amyotrophic Lateral Sclerosis Functional Scale- revised
FIM - Functional Independence Measure
FSS - Fatigue Severity Scale
MRCSS - Medical Research Concil sum score.
HR 65% - heart rate corresponded to 65% for aerobic training
RHR - Resting heart rate
VO^2 - Oxygen Consumption, ml/min/kg
6 MW - Six Minute Walk Test

Author's contributions

AM, FP and CA contributed to the conception and design of the project, the analysis and interpretation of data; in the editing of the work and in the critical review, in the final approval of the version to be published. AL and EG contributed to the conception and design of the project and the acquisition of and interpretation of data. MC and CG contributed to the analysis and interpretation of data ant to the editing of the work for the final approval of the version to be published.

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Conflict of Interest

The authors report no conflicts of interests.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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