IMPACT OF EXPIRATORY STRENGTH TRAINING IN AMYOTROPHIC LATERAL SCLEROSIS: RESULTS OF A RANDOMIZED, SHAM-CONTROLLED TRIAL

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ABSTRACT: *Introduction*: The purpose of this study was to determine the impact of an in-home expiratory muscle strength training (EMST) program on pulmonary, swallow, and cough function in individuals with amyotrophic lateral sclerosis (ALS). *Methods*: EMST was tested in a prospective, single-center, double-blind, randomized, controlled trial of 48 ALS individuals who completed 8 weeks of either active EMST (n = 24) or sham EMST (n = 24). The primary outcome to assess treatment efficacy was change in maximum expiratory pressure (MEP). Secondary outcomes included: cough spirometry; swallowing; forced vital capacity; and scoring on the ALS Functional Rating Scale—Revised. *Results*: Treatment was well tolerated with 96% of patients completing the protocol. Significant differences in group change scores were noted for MEP and Dynamic Imaging Grade of Swallowing Toxicity scores (P < 0.02). No differences were noted for other secondary measures. *Discussion*: This respiratory training program was well-tolerated and led to improvements in respiratory and bulbar function in ALS.

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Impaired swallowing, cough, and respiratory function are common in amyotrophic lateral sclerosis (ALS), accounting for 91.4% of mortality via malnutrition, aspiration, pneumonia, and neuromuscular respiratory failure.[1–5] Although the use of global exercise programs in ALS is still being explored, recent preliminary evidence suggests that mild-to-moderate intensity exercise, applied early in the disease, may have beneficial effects in both animal models[6–10] and humans.[11–22] As impaired airway defense mechanisms (dysfunctional expiratory phase of voluntary cough production) are associated with both dysphagia and tracheal aspiration in ALS,[23,24] management strategies that improve or maintain subglottic air-pressure generation, airway clearance ability, and peak cough flow may be beneficial.[25]

We recently reported improvements in maximum expiratory pressure (MEP) and swallowing kinematics after a well-tolerated 5-week exercise program targeting expiratory force generation, cough, and airway protection (expiratory muscle strength training, EMST) in 15 individuals with ALS.[20] This present double-blind, sham-controlled, randomized clinical trial extends these preliminary findings, testing our hypothesis that 8 weeks of daily, moderate-intensity resistance EMST at home, applied early in the course of ALS, will actively engage the expiratory and submental musculature, deter disuse atrophy, and prolong more effective cough function, airway protection, swallowing, and functional oral intake.

METHODS

Participants. Fifty-two individuals with a diagnosis of probable or definite ALS according to the revised El-Escorial criteria[26] were screened for potential enrollment in this study at the University of South Florida's ALS Center. The diagnosis was confirmed in all patients by academic neuromuscular neurologists specializing in ALS before screening for enrollment. Inclusion criteria were: (1) confirmed ALS diagnosis; (2) forced vital capacity > 65% predicted; (3) Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRS-R) score > 30; (4) adequate cognition to follow simple commands as evidenced by a score of >24 points on the Mini-Mental Status Examination[27]; (5) no allergies to barium; (6) no tracheostomy or mechanical ventilation; and (7) no diaphragmatic pacer. This study was approved by the university institutional review board and conducted in accordance with the Declaration of Helsinki. All included patients provided informed written consent.

Design. As noted, this study was a prospective, double-blind, randomized, sham-controlled clinical trial. Once enrolled, participants were assigned a study number and randomized to either the experimental group (EMST) or control (sham EMST) group. Baseline assessments of respiratory, swallow, and cough physiologic domains were performed, and participants immediately commenced the assigned 8-week treatment regimen. After treatment, participants were again assessed

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised; DIGEST, Dynamic Imaging Grade of Swallowing Toxicity; EAT-10, Eating Assessment Tool-10; EMST, expiratory muscle strength training; FOIS, Functional Oral Intake Scale; FVC, forced vital capacity; MEP, maximum expiratory pressure; PAS, Penetration–Aspiration Scale; VFSS, videofluoroscopic swallowing study

Key words: amyotrophic lateral sclerosis, cough, EMST, exercise, expiratory muscle strength training, rehabilitation, swallowing

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using the entire assessment battery. Figure 1 illustrates this timeline.

Randomization and Blinding. Participants were assigned to the EMST or control (sham EMST) group using a permuted block randomization schedule. Participants and the clinical researchers performing and interpreting evaluations were blinded to group assignment. Cough spirometry and videofluoroscopic data were de-identified and coded to blind participant identification and evaluation testing time-point. The home therapist was responsible for introducing and performing treatments with the appropriate respiratory trainers and was, therefore, knowledgeable on group assignment throughout the trial.

EMST Training Protocol. EMST was completed using a handheld, one-way, spring-loaded valve trainer. EMST was performed with the trainer set at 50% of the patient's individual maximum expiratory pressure (MEP), providing a moderate training load on the expiratory muscles. To accommodate individualized training loads with thresholds that ranged between 14 and 107 cm H_2O, 2 devices were utilized. Specifically, a lower resistance threshold trainer with a resistance load between 5 and 20 cm H_2O was used by participants whose MEPs were <40 cm H_2O (Philips Threshold PEP Trainer; Philips Respironics, Cedar Grove, New Jersey). For participants whose MEPs were >40 cm H_2O, a higher threshold trainer with a range of 20–150 cm H_2O was utilized (EMST 150; Aspire Products, Gainesville, Florida). Given that labial weakness is typical in ALS patients, a flanged rubber mouthpiece was attached to the opening of the expiratory trainer to facilitate labial seal during exercises. EMST therapy sessions were completed at home on 5 days of the patients choosing per week. During training, the participants sat in a comfortable position and wore a nose-clip to prevent air escape due to nasopharyngeal weakness. They took a deep breath, held their cheeks lightly (or had a caregiver do so), and blew forcefully into the training device. A single daily training session consisted of 25 targeted forced exhalations through the trainer, performed in 5 sets of 5 repetitions. This was described to participants as the "Rule of Fives" and has been used previously in other patient populations.[28] Participants were instructed to rest between each 5-breath set, and a typical training session lasted approximately 20 minutes. On the first training session of each week, a research therapist visited the patient in their home to reassess MEP using a handheld digital manometer (MP01 Micro Respiratory Pressure Meter; Micro Direct, Inc., Lewiston, Maine) and recalibrate the EMST trainer to represent 50% of the current MEP value. After this adjustment, each patient performed an EMST therapy session with the therapist. The remaining 4 daily therapy sessions were performed during the week at home with the assistance of the participant's caregiver. Patients therefore completed 125 targeted exhalations each week and a total of 1,000 exercise repetitions during the 8-week program. To encourage compliance and accountability, participants and their caregivers were provided with a home therapy log and asked to track daily therapy sessions by marking off each exercise set performed.

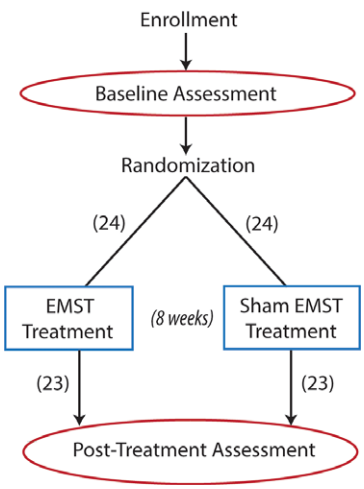

FIGURE 1. Study design flowchart. EMST, expiratory muscle strength training.

Sham Training Protocol. Patients assigned to the sham EMST group completed an 8-week training protocol with a trainer that looked identical to the high-physiological-load trainer (EMST 150), but had the internal spring removed. Therefore, these patients performed exercises against no physiological load. The training protocol was in every other respect identical to the EMST group.

Evaluation Procedures and Outcomes. Participants completed 2 comprehensive evaluations of pulmonary, cough, and swallowing function at baseline and immediately after the assigned 8-week training program. Both patients and evaluators were blinded regarding sham vs. active treatment.

Primary Outcome Measure: MEP. MEP was the primary outcome measure. It was assessed using the MP01 handheld digital manometer. To minimize labial leakage in patients who were unable to create a tight lip seal due to facial weakness, a flanged rubber mouthpiece was attached to the manometer. During MEP testing, the participant was seated with a nose-clip in place to occlude the nasal cavity. After inhaling to total lung capacity, participants were instructed to place their lips around the mouthpiece and blow out as forcefully as possible. Three trials were collected, and the highest obtained MEP was used in the analysis.

Swallowing Function. Three measures of swallowing function were obtained to assess: (1) global swallowing function; (2) oral intake; and (3) patient report.

Global Swallow Function. To examine physiological swallowing function, the "gold standard" videofluoroscopic swallowing study (VFSS) was performed. Participants were seated upright in a lateral viewing plane using a properly collimated Philips BV Endura fluoroscopic C-arm unit (GE OEC 8800 Digital Mobile C-Arm System, Type 718074). A Swallowing Signals Lab Unit (Pentax, Lincoln Park, New Jersey) digitally recorded the fluoroscopic images at 29.97 frames per second using a scan converter. A standardized bolus presentation protocol was used and consisted of two 1-ml boluses of liquid contrast agent (barium), one 3-ml bolus of thin liquid contrast, one 3-ml bolus of paste, one 20-ml bolus of liquid contrast, one 90-ml bolus of thin liquid contrast in the lateral view, and a 20-ml bolus of liquid contrast in the anterior/posterior view. To ensure patient safety, the VFSS was terminated immediately after a second aspiration event on any of the 7 swallow trials. Images were recorded digitally onto the swallow workstation (Pentax) for subsequent analysis.

The validated Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) was utilized to index global swallowing function.[29] The DIGEST includes a swallowing efficiency subscore (0–4), based on amount and frequency of pharyngeal residue, and a swallowing safety subscore (0–4), based on amount, depth, and frequency of penetration/aspiration. The total DIGEST score reflects the interaction between efficiency and safety subscores to yield a global grade of pharyngeal dysphagia (0 = normal swallowing function, 1 = mild dysphagia, 2 = moderate dysphagia, 3 = severe dysphagia, 4 = life-threatening dysphagia).[29] For statistical analyses, DIGEST scores ≥1 were classified as dysphagic and those <1 as non-dysphagic.

Airway safety was further evaluated using the validated Penetration–Aspiration Scale (PAS), an 8-point ordinal scale of airway safety that describes the degree of airway invasion, the participant's response, and whether the invasive material is successfully ejected from the airway.[30] Using previously defined thresholds for safe vs. unsafe swallowing, individuals whose PAS score was ≥3 were considered "unsafe" and those whose PAS was ≤2 were considered "safe" swallowers for data analysis purposes. All objective ratings were performed in a blinded fashion on all swallows and the worst PAS score was utilized for statistical analysis. A primary rater analyzed all VFSE data with a secondary rater scoring 25% of collected data for the purposes of reliability. If discrepancies were noted for either the PAS or DIGEST scores, a consensus meeting was held between raters with the option of a third expert rater available if consensus in scoring could not be met.

Daily Oral Intake. The Functional Oral Intake Scale (FOIS)[31] was used as an index of daily oral intake. This validated 7-point ordinal scale measures what foods an individual consumes to meet their daily nutritional and hydration requirements and ranges from a 1 (nothing by mouth) to 7 (full oral diet with no restrictions).

Patient Report. Finally, the Eating Assessment Tool-10 (EAT-10)[32] was administered as a patient-reported outcome (PRO) of swallowing function. The EAT-10 is a validated 10-item patient-rated questionnaire with each question rated on a 5-point ordinal scale. A total EAT-10 score ranges from 0 (indicative of no self-perceived swallowing impairments) to 40 (indicative of severe swallowing impairments). We have previously established that a cut-point of 8 on the EAT-10 distinguishes between ALS patients with dysphagia vs. those without dysphagia.[33] Therefore, in the current study, this threshold was utilized for statistical analysis.

Voluntary Cough Spirometry. Cough was assessed using an oral pneumotachograph (MLT 1000; ADInstruments, Inc., Colorado Springs, Colorado), connected to a spirometry mouthpiece filter (MQ 304 Spirometer Filter; Vacumed; Ventura, California) during voluntary cough production. Each participant was seated with a mouthpiece filter held in place by the examiner, nose-clips in place, and instructed to "cough hard like something is stuck in your throat." The patient was provided with an example by the examiner who ensured the patient understood the requirements of this task, and 3 trials were obtained. Airflow signal was measured, low-pass filtered at 60 Hz, digitized at 1,000 Hz, and displayed on a portable laptop computer using LabChart version 7 (Microsoft Corp., Redmond, Washington). Physiological voluntary cough airflow measures deduced from the cough flow waveforms included: (1) inspiratory phase duration (time from onset of inspiration after tidal volume breathing to the end of inspiration before the compression phase of cough); (2) inspiratory peak flow (peak inspiratory flow during the inspiratory phase preceding the cough); (3) compression phase duration (time from the end of the inspiratory phase to the beginning of the expiratory phase); (4) expiratory rise time (time from the beginning of expiratory phase to the peak expiratory flow); (5) expiratory peak airflow (peak airflow during the expiratory phase of the cough); and (6) cough volume acceleration (expiratory peak flow divided by expiratory rise time). Cough spirometry measures were assessed on the first cough epoch across the 3 trials (i.e., the first cough attempt for each of the 3 trials) by a blinded rater.

Forced Vital Capacity. Forced vital capacity (FVC) was assessed using a handheld spirometer (Micro I; Carefusion, Yorba Linda, California) in accordance with the American Thoracic Society guidelines. Percent predicted values for FVC were recorded and used for statistical analysis.

ALSFRS-R. The ALSFRS-R[34] was administered before and after treatment to index global disease progression. A total score was calculated as well as a respiratory subscale (out of 12) and bulbar subscale (out of 12) for comparative analysis.

Statistical Analysis. Baseline differences between groups were assessed by *t*-test (continuous outcomes) and chi-square test (categorical outcomes). To assess differences in pre to post change over time between groups in the primary outcome of MEP, linear regression models were used. These models included posttest scores as the outcome, and group status and pretest scores as the predictors. Using pretest scores as a predictor creates a "residual change score" relative to the outcome. If the effect of group status is statistically significant ($P < 0.05$), then it can be interpreted that the groups differed in their change from pre to post. The *F*-statistic (F), with numerator degrees and denominator degrees of freedom = 1 and 45, was used to test the statistical significance of between-group differences. In addition, the pretest score as a predictor controls for potential baseline performance differences was included. These analyses also controlled for other baseline covariates, including age, gender, disease-onset type, disease duration, and ALSFRS-R. This approach was also used for secondary outcomes that were continuously measured. For ordinal outcomes (DIGEST, PAS, FOIS, and EAT-10), previously determined clinical relevant cutoffs were used to dichotomize these variables: DIGEST > 1; PAS ≥3; FOIS ≤ 6; and EAT-10 > 8.[29,31,33] For these outcomes, logistic regression analyses were conducted in a similar manner to that described previously. Between-group differences were tested with likelihood-ratio chi-square test, with 1 degree of freedom; $P < 0.05$ considered statistically significant. Both raw and corrected *P*-values are reported for secondary outcomes. *P*-values were corrected for multiple comparisons using the false discovery rate approach.[35] All analyses were conducted by the study biostatistician using JMP Pro version 13.0 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Forty-eight individuals met the inclusion criteria and were enrolled in this study. Demographic details for this cohort are summarized in Table 1. Over the 2-month study period, 2 patients withdrew from the study (1 from each group). Reasons for withdrawal were: (1) diagnosis of cancer requiring immediate

Table 1. Patients' demographics for the entire cohort and the active and sham groups

	Entire cohort (N = 48)	Active group (N = 24)	Sham group (N = 24)	P-value*
Age (years)	61.6 (10.2)	63.1 (10.0)	60.1(10.3)	0.31
Gender (M/F)	29/19	17/7	12/12	0.14
Disease duration†	18.9 (11.4)	20.9 (14.5)	16.9 (6.8)	0.22
Onset (spinal/bulbar/mixed)	35/11/2	17/5/2	18/6/0	0.24

Data expressed as mean (standard deviation) or as number.

**Values are from* t*-tests for continuous measures and chi-square tests for categorical measures.*

†*Mean number of months from symptom onset.*

radiation and chemotherapy; and (2) patient no longer wished to participate. Adherence for completing prescribed exercises was excellent and ranged between 95% and 100% (between 950 and 1,000 completed repetitions). Patients' characteristics were well balanced across groups with no statistically significant baseline differences across treatment groups for any of the demographic variables (see Table 1). A summary of results is provided in Table 2.

Primary Outcome. For the primary outcome of MEP, there were no statistically significant baseline differences in MEP across treatment groups (see Table 2). Group status had a significant influence on change in MEP from pre to post time-points. Specifically, those in the active EMST treatment group demonstrated a significantly higher increase from pre- to posttreatment compared with those in the sham group (Fig. 2).

Swallowing. After a consensus meeting, rater agreement for DIGEST ratings was 100% without the need for a third expert rater. After adjusting for multiple comparisons, significant group differences between pre to post time-points were observed for global swallowing function (total DIGEST score) and the DIGEST efficiency subscale score. Little to no change occurred for ALS patients in the active group, whereas those in the sham group worsened from the pre to post time-points (Table 2). Although non-significant after adjusting for multiple comparisons, functional oral intake (FOIS scores) improved by 14.4% in the active group and worsened by 11.8% over the 2-month period in the sham group (Table 2). No group differences were observed in swallowing safety metrics (DIGEST safety subscore or PAS score) or in the patient-reported swallowing outcome (EAT-10).

Cough. After adjusting for multiple comparisons, no group differences were observed from pre to post time-points for cough spirometry measures (Table 2).

ALSFRS-R and FVC. No group differences were noted for ALSFRS-R scores or FVC (Table 2).

DISCUSSION

EMST was well tolerated and led to significant improvements in MEP (the primary outcome measure), as well as total DIGEST scores and DIGEST efficiency subscale scores. Clinically significant trends for maintenance or improvements in peak cough flow and oral intake, respectively, were also noted. No significant changes were noted in other measures of voluntary cough production, FVC, swallowing safety, patient report of swallow (EAT-10), and disease progression (ALSFRS-R).

This study extends the findings of our earlier pilot study that moderate intensity respiratory training using EMST is safe, feasible, and well-tolerated for early-stage ALS patients.[20] Our patient retention rate of 96% is not only higher than that of our earlier pilot trial, but also substantially better than retention rates in most ALS clinical therapeutic trials, possibly due to the convenience of home-based therapy, facilitated by weekly visits from a home therapist. On average, MEP increased by 25% for patients assigned to the active EMST group compared with a 6% increase in the sham group over the 8-week treatment period. The small increase in MEPs observed for the sham group may be due to a potential learning or familiarity effect of MEP testing procedures or due to variability of performing maximum pulmonary function tests and highlights the methodologic need for a comparison group in intervention-based clinical trials in ALS. Increased MEP for the EMST group supports our previous findings of a 29% increase in MEPs in 15 ALS patients after 5 weeks of EMST (compared with a 9% MEP reduction in these patients during a 5-week lead-in period). Furthermore, in the current study, 70% of patients (n = 16) in the active EMST group demonstrated increases in MEPs of >15%. These increases are encouraging and suggest that this simple, non-invasive, at-home training program may not only maintain, but also improve, function over the short term. Further work is needed to explore the long-term impact of this intervention.

Although becoming statistically non-significant after adjusting for multiple comparisons, of clinical significance was the finding that peak expiratory cough flow remained stable (0% change) for those

Table 2. Mean group values across pre- and post- testing time points with raw and adjusted P Values.

		ACTIVE GROUP:			SHAM GROUP:					
		Mean Pre (SD)	Mean Post (SD)	**Change*** (95% CI)	Mean Pre (SD)	Mean Post (SD)	**Change** (95% CI)	**F or χ^2 Value**	**Raw P Value**	**Corrected P Value**
	Maximum Expiratory Pressure (cmH20)	98.5 (45.7)	125.5 (61.3)	**25.5** (14.3,36.7)	89.8 (37.4)	96.6 (45.9)	**6.6** (-3.4,16.5)	7.5	0.009*	-
COUGH:	Inspiratory Peak Flow Rate (L/s)	-2.0 (1.1)	-2.3 (1.5)	**-0.4** (-1.0,0.2)	-1.7 (0.8)	-2.0 (1.0)	**-0.2** (-0.8,0.3)	0.8	0.38	0.61
	Peak Expiratory Flow Rate (L/s)	6.2 (2.8)	6.2 (2.7)	**0** (-1.3,1.3)	5.2 (2.4)	4.8 (2.4)	**-0.6** (-1.5,0.4)	5.2	0.03*	0.09
	Cough Volume Acceleration (L/s/s)	147.2 (92.2)	147.2 (78.5)	**-0.2** (-35.6,35.2)	121.0 (86.9)	114.9 (74.5)	**-11.9** (-36.1,12.2)	2.6	0.12	0.32
	Inspiratory Phase Duration (sec)	1.7 (0.8)	1.1 (0.7)	**-0.1** (-0.6,0.4)	1.4 (0.8)	1.4 (0.7)	**0.1** (-0.5,0.6)	1.1	0.30	0.59
	Expiratory Phase Duration (sec)	0.05 (0.03)	0.04 (0.02)	**-0.01** (-0.02,0.01)	0.06 (0.03)	0.06 (0.04)	**0** (-0.01,0.01)	1.7	0.20	0.46
	Compression Phase Duration (sec)	0.21 (0.11)	0.21 (0.10)	**0** (-0.05,0.04)	0.23 (0.12)	0.23 (0.14)	**0** (-0.05,0.05)	0.2	0.69	0.85
SWALLOWING:	**Global:** n=dysphagic (DIGEST>1) (% dysphagic)	2 (8.7%)	3 (13.0%)	**4.3%** **(-15.7,24.4)**	2 (10.5%)	6 (28.6%)	**18.1** **(-7.5,40.7)**	10.9	0.001*	0.02*
	Safety: n= unsafe (PAS>3) (% unsafe)	5 (20.8%)	4 (16.7%)	**-4.1%** **(-28.9,20.0)**	9 (37.5%)	5 (22.7%)	**-14.8%** **(-38.2,11.6)**	0.05	0.83	0.86
	Efficiency: n= inefficient (DIGEST-E>1) (% inefficient)	2 (8.7%)	3 (13.0%)	**4.3%** **(-15.7,24.4)**	2 (10.5%)	5 (23.8%)	**13.3%** **(-11.4,35.9)**	9.3	0.002*	0.02*
	Oral Intake, n= FOIS ≤ 6 (% FOIS ≤ 6)	10 (41.7%)	6 (27.3%)	**-14.4%** **(38.5,12.7)**	7 (29.2%)	9 (41.0%)	**11.8%** **(-14.9,35.6)**	4.6	0.03*	0.10
	EAT-10, n=EAT-10 > 8 (%, EAT-10 > 8)	7 (29.2%)	6 (27.3%)	**-1.9%** **(-26.4,23.4)**	7 (30,4%)	8 (36.4%)	**6.0%** **(-20.4,31.4)**	0.03	0.86	0.86
ALSFRS-R:	Total Score	36.6 (6.3)	35.7 (6.5)	**-1.3** (-3.1, 0.4)	37.5 (6.1)	35.9 (8.2)	**-2.1** (-3.7,-0.5)	0.24	0.63	0.84
	Respiratory Subscale	10.4 (1.8)	9.9 (1.7)	**-0.4** (-1.1,0.3)	10.0 (1.0)	10.5 (1.9)	**-0.7** (-1.7,0)	0.31	0.58	0.84
	Bulbar Subscale	10.3 (1.4)	10.1 (1.5)	**-0.1** (-0.5,0.3)	10.1 (1.6)	9.7 (2.3)	**-0.6** (-1.1,-0.30)		0.33	0.89
	Forced Vital Capacity: (% Predicted)	80.7 (10.0)	73.7 (19.7)	**-7.6** (-14.9,-0.3)	81.4 (16.2)	73.7 (18.4)	**-8.3** (-14.7,-1.9)	0.04	0.84	0.86

*Key: *Significant difference; F: F statistic with df = 1 (numerator), 45 (denominator); $\chi 2$: chi-square statistic with df = 1; ALSFRS-R: ALS Functional Rating Scale-Revised; DIGEST: Dynamic Imagine Grade of Swallowing Toxicity; FOIS: Functional Oral Intake Scale; EAT-10: Eating Assessment Tool-10.*

ALS patients performing active EMST exercises, yet decreased and became weaker for those who did not. This is particularly significant for individuals with ALS who commonly have difficulties with secretion management and excessive mucus build-up in the lower airways. Other studies have reported improvements in voluntary cough after EMST in Parkinson's disease,[36] multiple sclerosis,[37] and the sedentary elderly,[38] as well as in reflexive cough and urge-to-cough metrics after EMST in individuals with stroke.[39] Given that peak cough flow depends on expiratory pressure–generating forces, it is plausible that the increased MEPs in the active group afforded the maintenance of peak expiratory flow (i.e., cough strength) in the present study.

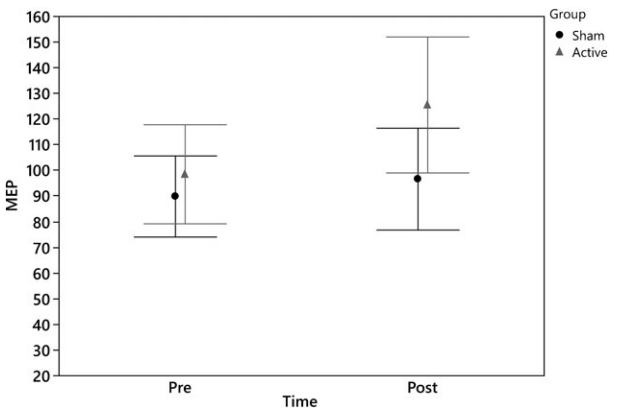

FIGURE 2. Mean (95% confidence interval) maximum expiratory pressure (MEP, cm H_2O) values for active (gray triangle) and sham (black circle) groups across time-points. Regression analysis for change scores denotes a significant group difference in change scores ($P < 0.05$).

No group differences were noted for swallowing safety in this study. However, given that our ALSFRS-R and FVC inclusion criteria were designed to enroll early to mid-stage subjects, and that specific impairments in swallowing safety were not part of our inclusion/exclusion criteria, our cohort had a relatively low incidence of unsafe swallowers (29%). In fact, less than one third of the participants were unsafe swallowers, with only 5 individuals in the active group (20%) being penetrator/aspirators, substantially limiting our ability to assess the impact of this intervention on swallowing safety. Group differences, however, were observed across time-points for global swallowing function (total DIGEST score) and swallowing efficiency (DIGEST efficiency subscale score) such that there was only a 4% increase in number of individuals demonstrating impaired DIGEST scores (>1) in the active group, whereas there was an 18% increase in

the sham group (i.e., this metric worsened in the sham group but remained relatively preserved in the EMST group). Previous studies have demonstrated that EMST facilitates repeated, submaximal, and load-dependent demands on the submental, lingual, palatal, velopharyngeal, and pharyngeal musculature.[40–43] Given that synchronous firing and coordination of these muscles is imperative for adequate pressure generation to facilitate bolus transport during swallowing, functional improvements or maintenance of swallowing safety and efficiency after EMST are physiologically supported. For example, coordinated activation of the extrinsic lingual muscles represent the main "pressure drivers" to transport the consumed bolus posteriorly, whereas the velopharyngeal and palatal muscles elevate and retract to seal the nasopharynx, to aid in pharyngeal pressure generation and subsequent bolus flow. Finally, the submental musculature facilitates superior and anterior laryngeal movement during deglutition, which is imperative for epiglottic inversion and adequate upper esophageal sphincter relaxation. Given the documented impact EMST is noted to have on the aforementioned bulbar musculature, it is possible that the repetitive application of a submaximal load on these muscles may have provided muscular conditioning for ALS patients enrolled in the active EMST group and contributed to maintenance of swallowing efficiency (i.e., the degree of residue remaining in the pharynx) and our global swallowing measure (total DIGEST score).

Nutrition is of the upmost importance in ALS, and malnutrition (due primarily to dysphagia) confers a 7.7-fold increased risk of death.[44] Although becoming statistically non-significant after correcting for multiple comparisons, a clinically meaningful finding was that 42% of active EMST group patients reported being on an altered or restricted diet at baseline that decreased to 27% posttreatment. In comparison, oral intake was noted to worsen in the sham group, with 29% of individuals reporting consumption of an altered or restricted diet at baseline that increased to 41% posttreatment. Future longer term studies should examine this more closely with measures such as body mass index, a known predictor of survival in ALS.[45–48]

No significant changes were noted for the global disease progression marker (ALSFRS-R). It is likely that a 2-month time period was not adequate to document disease-related progression or the potential impact of EMST on this metric. Future studies are needed to evaluate the impact of EMST on disease progression over longer intervals and additional important related variables including quality of life, hospitalization rates, aspiration pneumonia rates, time to ventilator, time to feeding tube dependence, and death. Similarly, no findings were noted for FVC. Given that the FVC maneuver is dependent on both inspiratory and expiratory muscle strength and capacity, it is not necessarily surprising given that the current intervention only targeted expiratory force generation, and not inspiratory muscle strength or volume recruitment observed with other therapies (e.g., lung volume recruitment). Future efforts may aim to determine the impact of a combined inspiratory and expiratory muscle strength training program or the differential or perhaps synergistic impact of lung volume recruitment therapies compared with respiratory strength training paradigms.

In conclusion, a mild-to-moderate intensity, 8-week, at-home EMST program was well tolerated in individuals with early ALS and resulted in significant improvements in MEP and oral intake, as well as maintenance of peak cough flow and swallowing function. Further studies are warranted to validate these findings and to investigate the long-term impact of this program on ALS disease progression.

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We (the authors) 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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