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A pilot study of the breath stacking technique associated with respiratory muscle endurance training in patients with amyotrophic lateral sclerosis: videofluoroscopic findings in the upper airway

Abstract

Introduction: Bulbar impairment represents a hallmark feature of amyotrophic lateral sclerosis (ALS) that significantly impacts survival and quality of life. Respiratory complications arise because of the weakness of the upper airway and respiratory muscles leading to respiratory failure, impaired swallowing, and reduced airway safety. Breath stacking and respiratory muscle endurance training are techniques that have been described to improve respiratory and bulbar function in patients with ALS. Considering the above, a respiratory technique named TR3 was developed. This study aimed to measure the acute effects of this technique on the upper airway through videofluoroscopy and to assess its clinical trial feasibility in patients with ALS.

Material and methods: In this cross-sectional study, we enrolled participants diagnosed with ALS to perform a single session of TR3. Epidemiological data and baseline assessments were collected. The assessments included kinematics from videofluoroscopy measuring the retropalatal airspace size, the size of the narrowest airway, and the pharyngeal area during rest and TR3.

Results: Eight participants were included. During TR3, an acute increase of 15% was observed in the retropalatal airspace size ($t = 5.14$, $p < 0.01$), a 123% increase was observed in the size of the narrowest airway ($t = -4.18$, $p < 0.001$), and a 277% increase was observed in the pharyngeal area ($t = -5.34$, $p < 0.001$).

Conclusions: During the intervention, TR3 showed acute effects in increasing pharyngeal constriction, pharyngeal expansion, retropalatal airspace size, and post-lingual narrowest airway size and is feasible for a larger research program. A clinical trial (NCT04226144) is already being conducted to assess the chronic therapeutic effects of this technique and its impact on the clinical evolution of ALS.

Key words: amyotrophic lateral sclerosis, videofluoroscopy, pharyngeal constriction, expiratory muscle strength training, rehabilitation

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Introduction

Bulbar impairment represents a hallmark feature of amyotrophic lateral sclerosis (ALS) that significantly impacts survival and quality of life [1]. Respiratory complications arise because of the weakness of the upper airway and respiratory

muscles leading to respiratory failure [1, 2]. The weakness of the pharyngeal muscles in patients with ALS can also lead to decreased pharyngeal pressure, impaired swallowing, decreased airway safety, and reduced pharyngeal constriction [3]. Thus, strategies to improve this impairment must be recommended [4].

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An example of this strategy is periodic lung expansion by breath stacking (BS) which has been described by Bach *et al.* [5]. This technique decreases basal atelectasis, maintains compliance of the lungs and the chest wall, and increases peak cough flow (PCF) and cough effectiveness. Another important strategy is respiratory muscle endurance training (RMET) [4]. A similar strategy has led to improvements in respiratory and bulbar function in patients with ALS [2]. The success of these techniques can be proven by demonstrating their effect on upper airway muscles.

Considering the above, Dorça *et al.* [6] developed a novel respiratory therapy named TR3. This therapeutic option, which has recently had its research protocol published, comprises three techniques with BS plus RMET. During its execution, this technique naturally increases the expansion of the upper airways by the effect of BS. However, the effects of adding RMET have not yet been studied. This study used videofluoroscopy in order to measure the acute effects of this technique on the upper airway of patients with ALS and to assess its clinical trial feasibility.

Material and methods

Study design and participants

The present article is a cross-sectional study approved by the HC/UFG Ethics Committee (Approval number 3981050-19/08/2018). Participants diagnosed with probable-definite ALS (revised El Escorial criteria) [2, 4–9] who were treated at the Tertiary Referral Center for Neuromuscular Diseases of Hospital de Apoio de Brasília, Brazil [7] were enrolled in this study. Informed consent was obtained from the subjects.

Inclusion and exclusion criteria

The eligibility criteria for this study were as follows: participants diagnosed with ALS, participants previously adherent to daily TR3 therapy for a minimum period of 12 weeks, participants older than 18 years of age with preserved cognition proven by a score of ≥ 24 points on the Mini-Mental Status Exam, participants not allergic to barium, participants who did not undergo a tracheostomy or invasive mechanical ventilation, participants who did not have a diaphragmatic pacemaker, and participants without a comorbid respiratory disease. Participants were excluded if they were pregnant or had a previous history of kidney, respiratory, or other concomitant diseases.

Intervention

TR3 was developed based on the previously published physiological and biological principles of ALS [1, 2, 4–6]. This technique (Table 1) was performed in a single session at a position of 90° and was always executed in the same sequence and by the same therapist. A bag-mask ventilation system (BMV) (Lumiar, Brazil) with an inflated oro-nasal mask (Lumiar, Brazil) or mouthpiece (Respironics, USA) was used with a manometer (LiteSaver, Mercury Medical, USA) to monitor the optimal inspiratory pressure of 30 cmH₂O (Figure 1C). The regular BMV one-way valve was changed to a unidirectional valve with a positive end-expiratory pressure of 8 cmH₂O (VUP, Vent-Logos, Brazil) (Figure 1A, 1B). Details of the technique can be seen in Figure 1D and Supplementary Video 1.

The sequence of the technique adopted for TR3 was defined based on the empirical muscle

Table 1. Description of TR3 respiratory training program

Technique	Summary	BMV adaptations	Methods
VUP breath stacking	Detailed information about this protocol was recently described by Dorça <i>et al.</i> [6]. It consists of the BS technique [5] in addition to RMET [2, 3]	Unidirectional valve with positive end-expiratory pressure (VUP, Vent-Logos, Brazil) was used. Resistance was set to 8 cmH ₂ O	BS until IOP (set at 30 cmH ₂ O), holding air in the lungs for five seconds followed by blowing out the air with counter resistance (set at 8 cmH ₂ O) during all expiratory phase
PA	PA consists of lung insufflation with BMV until reaching IOP followed by a five-second valsalva maneuver	VUP-valve was set totally closed to avoid depressurization	BS until reaching IOP, holding air in the lungs for five seconds while performing valsalva maneuver. During the expiratory phase, patients blow out passively
PS	PS consists of lung insufflation with BMV until reaching IOP for five seconds followed by an effortful swallow maneuver [8]	VUP-valve was set totally closed to avoid depressurization	BS until reaching IOP, holding air in the lungs for five seconds followed by an effortful swallow maneuver. During the expiratory phase, patients blow out passively

BMV — bag mask ventilation; BS — breath stacking; IOP — inspiratory optimal pressure; PA — pressurized apnea; PS — pressurized swallowing; RMET — respiratory muscle endurance training

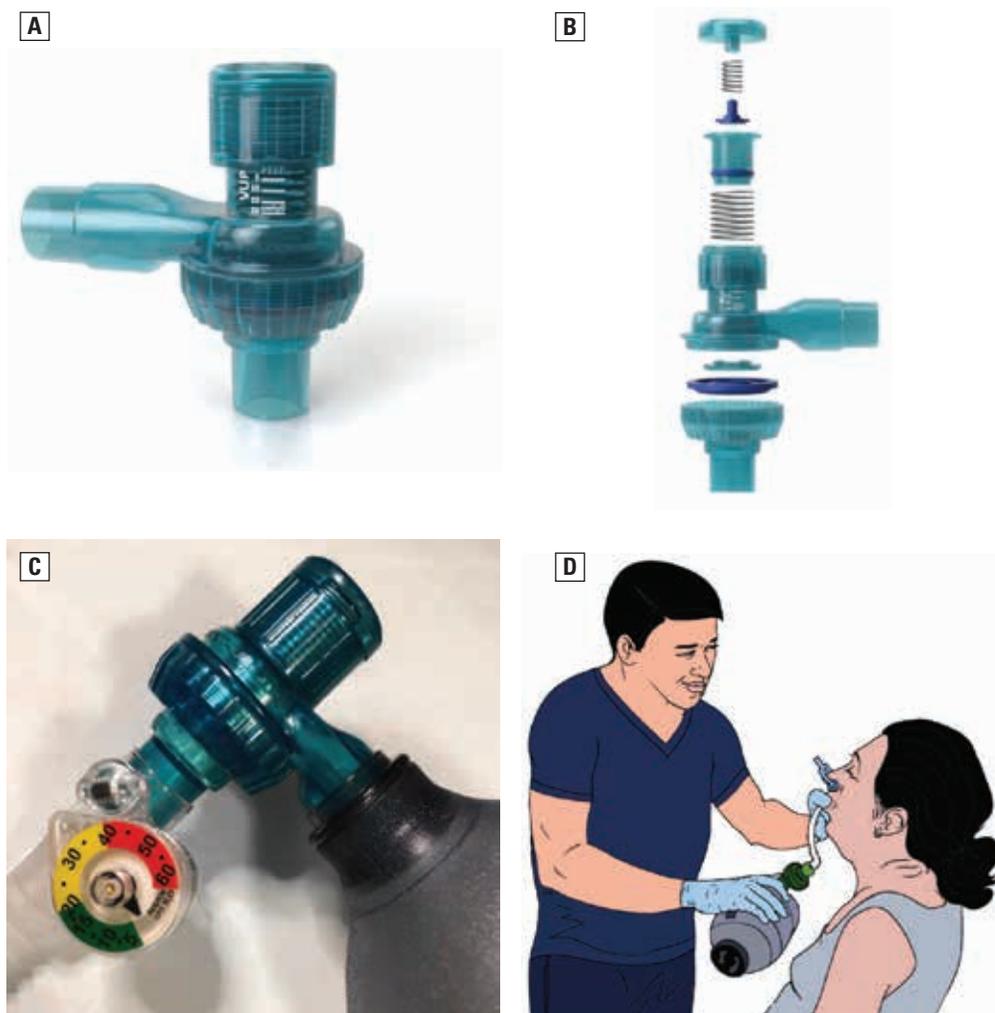


Figure 1. Details of novel materials used in TR3 respiratory training program. **A.** Unidirectional valve with positive end-expiratory pressure (VUP, Vent-Logos, Brazil); **B.** Disassembled VUP valve; **C.** Bag-mask ventilation mounted with a VUP valve and manometer; **D.** Example of technique execution [A, B — Ventlogos, Brazil, with permission]

recruitment level of each technique. The first was VUP [6], a technique that involves RMET [3] and BS [5, 6]. This was chosen because the patient blows against a resistance of 8 cmH₂O during the expiratory phase which demands high muscle recruitment in the upper airway. In this pilot study, the valve resistance was empirically set at 8 cmH₂O for all participants because it is a value slightly above the expiratory positive airway pressure usually used in non-invasive ventilation employed in the treatment of patients with ALS [1, 7]. The second technique, known as pressurized apnea, does not require RMET. It recruits the diaphragmatic and intercostal muscles. The third technique, named pressurized swallowing, also does not require RMET but contains an effortful swallowing maneuver [8]. It is intended to increase pharyngeal pressure by swallowing and push-

ing with sufficient force to facilitate clearance. Pressurized swallowing was chosen as part of TR3 with the aim of recruiting swallowing muscles and facilitating pulmonary secretion management.

Epidemiological data and baseline assessment

Epidemiological data were collected as follows: age, sex, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSF_{RS}-R) score [1, 2, 4–6, 9], and duration of adherence to previous TR3 treatment (in weeks). Additionally, pulmonary function tests were performed prior to the intervention. Spirometry was performed according to the method described by Pirola *et al.* [9] using a MIR Minispir (Minispir, USA) in compliance with the American Thoracic Society and European Respiratory Society guidelines. Sponta-



Figure 2. Details of key videofluoroscopic frames of interest analyzed. Overview of differences across pharyngeal constriction area during rest and during respiratory training. **A.** Example of rest position in which pharyngeal area at rest measurements were made; **B.** Example of maximum pharyngeal expansion (MPE) during VUP technique; **C.** Example of maximum pharyngeal constriction (MPC) during VUP technique

neous PCF was measured using a hand-held peak flow meter (Vitalograph, Ireland).

Outcomes (kinematic variables)

Standardized videofluoroscopic images were obtained using the OEC 9900 Elite Mobile C-arm (GE Healthcare, USA) and processed in the DICOM format using RadiAnt DICOM Viewer 2020 (Medixant, Poland). All analyses were performed at two different instances: while TR3 was being performed and during rest. These were reviewed frame by frame by two trained research assistants to identify three keyframes of interest: rest position, maximum pharyngeal constriction, and maximum pharyngeal expansion (Figure 2). To correct for any differences in pharyngeal size across participants, the pharyngeal constriction area (PCA) measurements were normalized using an anatomical scalar (squared C2-C4 vertebral distance) that has been previously described by Stokely *et al.* [10]. A free-hand tool was used to obtain the unobliterated pharyngeal space area (represented by air) in cm^2 . Values during swallowing (from hyoid and laryngeal displacement to rest) [11] were not considered in these analyses. The following kinematic variables were considered:

- **Pharyngeal area (PA) at rest:** defined as the pharyngeal area in cm^2 when the participants were in a seated position breathing gently (Figure 2A);
- **Maximum pharyngeal expansion (MPE):** defined as pharyngeal area in cm^2 during maximal pharyngeal expansion (Figure 2B);
- **Maximum pharyngeal constriction (MPC):** originally described by Stokely *et al.* [10], this has been used as a reference point in previous studies on kinematics [12, 13]. It is

defined as the pharyngeal area (Figure 2C) where the smallest amount of unobliterated air space is visible in the pharynx [10]. This value was considered to be zero in cases where the pharynx was fully constricted;

- **Retropalatal airspace size (RAS):** defined as the distance in cm between the uvular tip and the posterior pharyngeal wall [13];
- **Narrowest airway (NA):** defined as the point on the posterior pharyngeal wall where the post-lingual airway is narrowest, measured in centimeters [13].

RAS and the NA were measured during each key kinematic moment and considered as separate variables during rest (RAS_{rest} , NA_{rest}), during MPE (RAS_{max} , NA_{max}), and during MPC (RAS_{min} , NA_{min}).

Range variables for each technique were considered according to the following formulae:

- $\text{RAS}_{\text{range}} = \text{RAS}_{\text{max}} - \text{RAS}_{\text{min}}$;
- $\text{NA}_{\text{range}} = \text{NA}_{\text{max}} - \text{NA}_{\text{min}}$;
- Pharyngeal constriction range (PCR) = MPE – MPC.

Sample size

Considering that one of the objectives of this study was to assess the feasibility of this respiratory technique in a future clinical trial [6], 20% of the calculation of the ideal sample size ($n = 42$) proposed in the original protocol [6] was considered. In the original study conducted by Dorça *et al.* [6], sample size calculations were performed based on a meta-analysis conducted by Silva *et al.* [14]. Additionally, considering the low prevalence of disease, the present study's sample size was selected based on a reasonable estimate of the number of available participants that would meet the eligibility criteria during the planned 3 month study period. The choice of the sample

Table 2. Summarized results of RAS, NA size, and PA ranges during TR3

Key frame of interest	RAS ^a [cm]	RAS ^b [%]	NA ^a [cm]	NA ^b [%]	PA ^a [cm ²] ^c	PA ^b [%]	
During rest	1.10	—	0.80	—	4.55	—	
MPE during TR3	1.50 (1.10–2.25)*	+36%	1.73 (1.11–2.21)*	+116%	9.54 (8.04–11.70)*	+109%	
	(t = -2.82, p = 0.02)**		(t = 5.90, p < 0.001)**		(t = 7.54, p < 0.001)**		
MPC during TR3	0.23 (0–1.23)*	-37%	0.13 (0–0.44)*	-83%	2.54 (0.97–6.69)*	-44%	
	(t = 5.14, p < 0.01)**		(t = -4.18, p < 0.001)**		(t = -5.34, p < 0.001)**		
Total PCR ^a PCR = MPE – MPC	—	1.27	+15%	1.60	+123%	7.00	+277%

^aAverage. ^bDifference between rest; ^cC2–C4 squared pharyngeal area; *Range; **Paired t-test comparing variables RAS, NA and PCA during TR3 execution on the kinematic keyframes MPE and MPC to values observed during rest. MPC — maximum pharyngeal constriction; MPE — maximum expansion; NA — narrowest airway; PA — pharyngeal area; PCR — pharyngeal constriction range; RAS — retropalatal airspace size; TR3 — Respiratory Training Program

size was also supported by previous similar pilot studies in the ALS population [15–17].

Statistical analysis

Descriptive statistics were performed for disease demographics. Paired-sample *t*-tests were conducted on the following variables: retropalatal airspace size, narrowest airway, pharyngeal constriction area during maximum pharyngeal expansion, and maximum pharyngeal constriction. These tests were compared to values observed during rest (alpha = 0.05). Pearson’s correlation was conducted to explore correlations between age, ALSFRS-R, pulmonary function test results, and kinematic variables. All statistical analyses were completed using SPSS Statistics (IBM, Version 24) with statistical significance set at *p* < 0.05.

Results

Eight participants with a diagnosis of probable-definite ALS were included in this study. Epidemiological data regarding the study population were as follows: 62.5% were males (5 males and 3 females), average age was 51 years (range: 28–73 years), average ALSFRS-R score was 28 (range: 6–40), average forced vital capacity (FVC) was 57% (range: 8–87%), and average PCF was 330 L/min (range: 21–650 L/min). None of the epidemiological data had a statistically significant correlation with videofluoroscopic kinematic variables. The participants performed TR3 for an average of 21 weeks before the videofluoroscopic assessment.

During rest, participants presented with an average pharyngeal area of 4.55 cm², a retropalatal airspace size of 1.10 cm, and a narrowest airway size of 0.80 cm. During TR3, a 15% acute increase in retropalatal airspace size was observed (t = 5.14, *p* < 0.01). Further, a 123% increase in narrowest airway size (t = -4.18, *p* < 0.001) and a 277% increase in pharyngeal area (t = -5.34, *p* < 0.001) was also observed.

Considering pharyngeal constriction and expansion in the techniques studied, pressurized swallowing showed the greatest pharyngeal expansion, and pressurized apnea showed the greatest pharyngeal constriction. The average maximum pharyngeal expansion values observed during each technique were as follows: pressurized swallowing was 8.25 cm², VUP was 7.86 cm², and pressurized apnea was 7.42 cm². The average maximum pharyngeal constriction values for each technique were as follows: pressurized apnea was 4.01 cm², pressurized swallowing was 3.76 cm², and VUP was 3.58 cm².

Considering the videofluoroscopic kinematic variables during each technique, VUP showed the greatest changes in pharyngeal constriction (the difference between maximum expansion and maximum constriction). Pressurized swallowing showed the greatest changes in retropalatal airspace size and narrowest airway size. VUP presented an average pharyngeal constriction range of 4.85 cm², retropalatal airspace size range of 0.32 cm, and narrowest airway size range of 0.89 cm. Pressurized apnea presented an average pharyngeal constriction range of 4.06 cm², retropalatal airspace size range of 0.41 cm, and

narrowest airway size range of 0.75 cm. Pressurized swallowing presented an average pharyngeal constriction range of 4.81 cm², retropalatal air-space size range of 1.10 cm, and narrowest airway size range of 1.03 cm.

Summarized results of retropalatal airspace size, narrowest airway size, and pharyngeal constriction range are shown in Table 2.

Discussion

This is the first experimental study showing the effects of a respiratory technique on the upper airway using videofluoroscopy. It showed acute effects in increasing pharyngeal constriction, pharyngeal expansion, RAS, and post-lingual NA during the intervention. As a result of these effects, it proved to be feasible for a clinical trial.

The main limitations of the study are the sample heterogeneity, the small sample size, and the absence of electromyographic monitoring which would allow for a better understanding of the effects of the intervention on muscle recruitment. However, the use of videofluoroscopy allowed for greater precision in analyzing the spaces of the upper airway, which was the main objective of this study.

Several studies have used videofluoroscopy to assess quantitative videofluoroscopic measurements in patients with ALS. However, only swallowing outcomes were addressed [3, 18]. Pharyngeal airway changes have been assessed in the context of obstructive sleep apnea [13] but never in a respiratory investigation. As an alternative for measuring the strength of pharyngeal contraction, Leonard *et al.* [19] developed a pixel-based measurement system using lateral view videofluoroscopic study frames in the context of swallowing studies [10]. Pearson *et al.* [20] developed a method for objectively measuring pharyngeal spaces and normalized it using the C2-C4 anatomical scalar, thus reducing artifacts attributable to participant height [1, 21]. Recently, Stokely *et al.* [10] incorporated anatomical scaling into pixel-based measures of pharyngeal constriction which were based on single-frame measurements. This study supported the present study's methods.

No correlations were observed between pharyngeal spaces and pulmonary function tests performed in the study sample. However, despite the clinical heterogeneity, all participants included had been performing the TR3 regularly for a long time. It raises the possibility that these types of breathing exercises could positively im-

prove respiratory outcomes or act as an adjuvant to maintain pharyngeal spaces, even in poor respiratory conditions (low FVC/forced expiratory volume in 1 s). Considering the performance of each breathing exercise on kinematics, pressurized swallowing showed the greatest pharyngeal expansion and the greatest changes in RAS and NA. Pressurized apnea presented the greatest pharyngeal constriction. VUP showed the greatest changes in pharyngeal constriction.

The efforts adopted in understanding the effect of this single-session breathing exercise on patients with ALS are justified considering the importance of upper airway spaces in ventilation [1, 7]. Researchers hypothesize that the maintenance of these spaces could improve the clinical evolution of ALS concerning respiratory and swallowing outcomes, in line with previous results obtained by Waito *et al.* [3]. However, the immediate effect of session-based breathing exercises is insufficient to predict long-term results.

Considering the study results on acute upper airway constriction and expansion, the authors consider that this breathing exercise may have the potential to play a role in ventilation and may serve to improve outcomes in patients with weakness of the pharyngeal muscles [1] (which can cause decreased pharyngeal pressure) [3] and/or impaired swallowing (which compromises airway safety in patients with ALS) [2, 7]. The efficacy of TR3 performed systematically in a therapeutic context is a key outcome to be assessed in further investigations.

Conclusions

TR3 showed acute effects in increasing pharyngeal constriction, pharyngeal expansion, RAS, and post-lingual NA during the intervention and is feasible for a larger research program. A clinical trial (NCT04226144) is already being conducted to assess the chronic therapeutic effects of this technique and its impact on the clinical evolution of ALS.

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Conflict of interest

None declared.

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