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Swallowing outcome to speech therapy intervention in resistant hypertensive patients with obstructive sleep apnea

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Abstract

Purpose To evaluate (i) the outcome of swallowing therapy program on the rehabilitation of oropharyngeal dysphagia in resistant hypertensive patients with obstructive sleep apnea (OSA) and (ii) the association between the clinical and anthropometric characteristics of these individuals and this outcome.

Methods This was a prospective interventional study in which resistant hypertensives diagnosed with OSA by polysomnography and dysphagia by fiberoptic endoscopic evaluation of swallowing (FESS) participated. All participants underwent a FEES and assessment of the risk of dysphagia (Eating Assessment Tool, EAT-10) and swallowing-related quality of life (Swal–QoL) before and after the intervention. The therapeutic program was performed daily by the participants, with weekly speech-therapist supervision for eight weeks, including the following strategies: Masako, chin tuck against resistance, and expiratory muscle training.

Results A total of 26 (78.8%) of the participants exhibited improvement in the degree of dysphagia in the intervention outcome. After the intervention, there was a statistically significant improvement in the level of penetration–aspiration (p=0.007), the degree of pharyngeal residue (p=0.001), the site of onset of the pharyngeal phase (p=0.001), and the severity of dysphagia (p=0.001) compared to before intervention. The EAT-10 score was 2 (0–6) before and 0 (0–3) after intervention (p=0.023). Swal–QoL had a score on the symptom frequency domain of 92.8 (75–100) before and 98.2 (87.5–100) after intervention (p=0.002).

Conclusions Resistant hypertensive patients with OSA showed improved swallowing performance after swallowing therapy program.

Keywords Dysphagia · Deglutition disorders · Speech therapy · Resistant hypertension · Obstructive sleep apnea

Introduction

The current increases in life expectancy and obesity have made resistant hypertension (RHT) increasingly prevalent, characterized by the absence of blood pressure control

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swallowing disorder by 2.1 times [2]. Equally strong is the association established between RHT and obstructive sleep apnea (OSA) [3]. OSA is characterized by frequent upper airway collapses that cause periodic episodes of apnea and hypopnea [4], which condition may be associated with oropharyngeal dysphagia [5]. Commonly underdiagnosed in this population, interference with swallowing dynamics is evidenced through instrumental swallowing tests, such as those based on videofluoroscopy and fiberoptic endoscopic evaluation of swallowing (FESS) [6-11]. The frequent episodes of apnea and hypopnea lead to oxyhemoglobin desaturation, which interferes with the proper synchrony between swallowing and breathing functions [12, 13]. Snoring can also cause neurogenic and muscle changes in the upper airways of these patients [8, 14, 15] and a consequent reduction of oropharyngeal sensitivity. This impairment may translate into a deficit of oral sensorimotor control, impaired swallowing reflex, premature spillage, delayed onset of the pharyngeal phase, piecemeal deglutition, pharyngeal residue, penetration-aspiration [6-8, 11, 16-18].

Speech therapy is an alternative to conservative treatment for OSA. Its effect is to remodel the upper airways by strengthening the muscles responsible for maintaining this patent pathway during sleep, thereby combatting the symptoms of OSA by lessening snoring, alleviating daytime sleepiness, and improving the subjective quality of sleep [19]. Despite extensive scientific literature on speech therapy in the treatment of OSA and descriptions of swallowing impairment in OSA patients, no studies have investigated swallowing therapy program for the treatment of oropharyngeal dysphagia in patients with OSA.

Thus, the present study aims to evaluate the outcome of swallowing therapy program on the rehabilitation of oropharyngeal dysphagia of resistant hypertensives with OSA through FEES, a self-assessed instrument of the risk of dysphagia and the effect of swallowing on quality of life, and the evaluation of any associations between the clinical or anthropometric characteristics of these individuals and the outcome of swallowing changes after the intervention.

Methods

This was a prospective, longitudinal, interventional study, conducted between August 2017 and December 2019, enrolling individuals with RHT followed up in the Hypertension Program of a university hospital who were diagnosed with OSA and oropharyngeal dysphagia. The study was approved by the research ethics committee of the institution. All participants were volunteers and signed an informed consent form.

The diagnosis of OSA was made by means of all-night polysomnography test, initially performed between 2010

and 2013 and later in 2018. FEES was performed at the Otorhinolaryngology Service of university hospital, between February 2016 and December 2019. In the period between February 2016 and March 2018, resistant hypertensives with OSA were invited to participate in the study in which individuals with and without oropharyngeal dysphagia were identified as described [11]. Those who were diagnosed with dysphagia were selected for the present study, submitted to the swallowing therapy program, and re-evaluated between October 2017 and December 2019.

The study included individuals aged between 18 and 65 years of both sexes who were diagnosed with RHT, OSA confirmed by all-night polysomnography, and oropharyngeal dysphagia found by FEES. Exclusion criteria were individuals with neurological disease, craniofacial malformation, head and neck cancer, tracheostomy, vocal fold paralysis, chronic obstructive pulmonary disease, or surgery or radiotherapy in the head and neck area due to the risk of impaired swallowing function; individuals with cognitive or behavioral disorders that prevented the performance of the study procedures; individuals with no capacity for oral feeding; and individuals who did not adhere to the therapput program (lower than 85% implementation of the therapeutic plan proposed in the study).

Of the 155 patients with RHT identified, 70 were excluded after applying the eligibility criteria (Fig. 1). Of the 86 eligible individuals, 85 underwent FEES, and 58 (68.2%) were diagnosed with oropharyngeal dysphagia. After applying the exclusion criteria, 44 subjects underwent speech therapy, but only 33 completed all stages of the study, who made up the sample for analysis.

Polysomnography

The full-night polysomnography was performed in the sleep laboratory of the university hospital using the BrainNet BNT Poly polygraph and was supervised by a qualified professional. During the examination, the electroencephalogram (EEG), electrooculogram (EOG), submental electromyogram (EMG), nasal airflow, oximetry, respiratory effort, electrocardiogram, and anterior tibial electromyogram were recorded. The examination was complemented with video monitoring. Individuals who slept less than 240 min on the night of the study were excluded. The examination report was prepared by the same medical professional, a specialist in sleep medicine qualified by the Brazilian Association of Sleep Medicine and certified in sleep medicine by the Brazilian Society of Pneumology and Tisiology, who was unaware of the clinical data of the individuals.

The presence of apnea was defined by an apnea–hypopnea index (AHI) of > 5 events/hour, which was stratified into mild apnea (AHI = 5-14/hour), moderate apnea (AHI = 15-30/hour), and severe apnea (AHI > 30/hour) [4].

Fig. 1 Flowchart of study participants



Fiberoptic endoscopic evaluation of swallowing (FESS)

FEES was performed by a specialized and experienced otorhinolaryngologist and speech therapist. We have described the methods of the evaluation in detail [11]. Briefly, to perform the examination, the patient was positioned sitting at 90°, using a flexible Machida nasofibroscope (model ENT-30PIII). Two aliquots were given for each volume of 5 ml, 10 ml, and 15 ml in the consistencies of fine liquid, nectar, honey, and pudding, as well as 30 ml of fine liquid. The thickener Resource® Thicken Up Clear (Nestlé) was used to prepare the viscosities used. The food was stained with blue food dye for better visualization of the bolus.

All tests, before and after the swallowing therapy program, were recorded on a portable computer using the *Easy Cap* video capture card for later real-time and frame-byframe analysis with *Virtual Dub* software version 1.10.4. Two speech therapists experienced dysphagia independently and blindly evaluated the results. A third evaluator was consulted in case of disagreement.

The following were analyzed in the FEES records: premature spillage, onset of the pharyngeal phase, number of swallows, level of penetration-aspiration, and degree of pharyngeal residue. The site of onset of the pharyngeal phase was analyzed using the scale suggested by Baijens [20]. Since the onset of the pharyngeal phase occurs more frequently when the bolus head is in the posterior region of the mandibular ramus or in the vallecula [21], score > 1 was considered delayed onset of the pharyngeal phase. The level of penetration-aspiration was measured using the scale proposed by Rosenbek [22]. Though the original scale considered level 2 as penetration, studies indicate that this condition is found in healthy individuals [23], so penetration was considered present when the score was > 2. The degree of pharyngeal residue was measured using the scale proposed by Neubauer, Rademaker, and Leder [24]. Pharyngeal residue was considered present with a score ≥ 2 . The degree of dysphagia was determined according to the scale proposed by O'Neil [25], in which a lower score meant worse severity of dysphagia: (1)

severe dysphagia, (2) moderate to severe dysphagia; (3) moderate dysphagia; (4) mild to moderate dysphagia; (5) mild dysphagia; (6) functional swallowing; and (7) normal swallowing. Dysphagia was considered present with a score < 6.

Clinical evaluation

Sociodemographic information and anthropometric measurements were collected, such as sex, age, weight, height, body mass index (BMI), neck circumference, use of continuous positive airway pressure (CPAP), and smoking. In addition, the Brazilian versions of the self-assessment instruments for dysphagia risk, EAT-10 [26], and swallowingrelated quality of life, Swal–QoL [27], were applied before and after the therapy program. These two instruments were applied by a speech therapist specialized and experienced in the management of the protocol, who read the questions and marked the responses of the participants due to the socioeducational profile of patients treated at this hospital.

- Swallowing-related quality of life (Swal–QoL): an instrument that measures the impact of feeding difficulties in the daily life of individuals. It has 11 domains evaluated from 0 to 100. The closer to the maximum value, the more positive the self-perception of the subject in terms of the swallowing-related quality of life [27].
- Eating Assessment Tool, EAT-10: a screening instrument used for the detection of swallowing disorders, with multidisciplinary applicability. It consists of 10 questions evaluated from 0 to 4, in which 0 means there is no problem and 4 means there is a very large problem. The cutoff score for the risk of dysphagia is 3 points, indicating that a total score ≥ 3 is suggestive of dysphagia [26]. The evaluation covers three functional domain items ("Swallowing liquids requires an extra effort"; "Swallowing solids requires an extra effort"; "Swallowing pills require an extra effort"); three emotional domain items ("My swallowing problem interferes with my ability to eat away from home"; "The pleasure of eating is affected by my swallowing problem"; "Swallowing is stressful"); and four physical domain items ("My swallowing problem has resulted in weight loss"; "Swallowing is painful"; "When I swallow, food sticks in my throat"; "I cough up when I eat").

Swallowing therapy program

The therapy program lasted 8 consecutive weeks, with weekly meetings lasting 30 min, under the supervision of an experienced speech therapist and specialist in dysphagia. The patients were instructed to perform a daily therapeutic program that consisted of three exercises: Masako, chin tuck against resistance, and expiratory muscle training. The oropharyngeal exercises were selected mainly to promote muscle training for mechanical adjustment of the swallowing dynamics based on the clinical observation of the patients. All study participants received an individual kit with the instruments that were used in the therapeutic program: an inflatable rubber ball, a respiratory stimulator (Respiron Classic®), a nasal clip, and a table for daily recording of the performance of each proposed exercise. At the end of the 8 weeks of speech therapy, the participants were reassessed. The guidelines for performing the selected exercises are as follows:

- Masako: Protrude the tongue as much as possible and swallow with it positioned between the teeth. Three series of 15 swallows were assigned.
- Chin tuck against resistance: Press toward the chest an inflatable rubber ball, approximately 12 cm in diameter, positioned on the neck, between the chin and the sternum/manubrium region of the chest. The orientation consisted of properly positioning the ball on the neck and keeping the head flexed while pressing with force for 60 s and returning to the initial position for another 60 s. Five series of 1 min each were assigned.
- Expiratory muscle training: Put the nasal clip on the nose and the mouthpiece on the lips, with the respiratory stimulator in the inverted position. Blow out a short and strong breath to raise the three spheres of the device. They were told to perform 15 repetitions in three different head positions (forward, right, and left) and to rest for 1 min before changing the direction of the head.

Statistical analysis

Statistical analysis was performed with SPSS 19.0. Categorical data are presented as absolute frequencies and relative frequencies. The numerical data are presented as the mean and standard deviation in the case of a normal distribution or the median and interquartile range in the case of a nonnormal distribution. The distribution of the data was assessed by the Shapiro–Wilk test and a histogram.

To compare the categorical data before vs. after the swallowing therapy program, the McNemar chi-squared test was used. In case we could not perform the McNemar chisquared test, because the data were classified as qualitative/ ordinal, the marginal homogeneity test was applied, corresponding to an extension of the McNemar test. To compare the numerical data before vs. after the swallowing therapy program, the paired-samples *t* test or the Wilcoxon signedrank test was used, according to the need for a parametric or nonparametric test, respectively.

To assess the association between the clinical and anthropometric characteristics of the participants and the outcome of the swallowing changes after the therapy program, the participants were divided into two groups: (I) improved or remained unchanged after the intervention and (II) worsened after the intervention. Regarding categorical data, Pearson's chi-squared test or, in the case of cells with a frequency lower than five, Fisher's exact test was used. Regarding the numerical data, the t test of independent samples was used in case of normally distributed data or the Mann–Whitney test in case of nonnormally distributed data.

The indication of the parametric test followed the satisfaction of the premise of normality of data distribution in both groups. In addition, the homogeneity of variance was verified using the Levene test. The level of statistical significance adopted was 5% (p < 0.05).

Results

A total of 58 individuals were included in the study, of whom 33 completed the entire protocol. In the final sample, 30.3% were male, and the median age was 61 (56–64) years. Table 1 compares the baseline characteristics of participants with oropharyngeal dysphagia by FEES who completed the

entire study protocol vs. those who were excluded during the study. There was no significant difference in baseline characteristics between these two groups.

Table 2 shows the findings of the FEES before and after swallowing therapy program. After therapy occurred a statistically significant improvement in the level of penetration–aspiration, the degree of pharyngeal residue, the onset of the pharyngeal phase, and the severity of dysphagia compared to before therapy. That is, there were statistically significant reductions in the prevalence of penetration–aspiration, pharyngeal residue, and delayed onset of the pharyngeal phase after the intervention, and there was a statistically significant increase in the number of swallows after the intervention. Although the prevalence of premature spillage after the intervention decreased, this was not significant.

No adverse effects were observed during the execution of FEES. The agreement of the videoendoscopic findings between the evaluators was high: delayed onset of the pharyngeal phase (k=0.88), scale of the onset of the pharyngeal phase (k=0.74), pharyngeal residue (k=0.91), degree of pharyngeal residue (k=0.80), premature spillage (k=0.75),

Table 1 Characteristics of the ndividuals who completed the study vs. those excluded during	Cha
he study	.

Characteristics	All participants	Completed all sta	Completed all stages of study		
	(<i>n</i> =58)	Yes (n=33)	No (n=25)		
Sex, % male	14 (24.1%)	10 (30.3%)	4 (16%)	0.207 ^a	
Age (years)	61 (55–63)	61 (56–64)	60 (52-62)	0.126 ^b	
Weight (Kg)	82 (72.8–99.5)	86.8 ± 17.9	83.1±16.8	0.421 ^c	
Height (m)	1.61 (1.54–1.68)	1.62 ± 0.1	$1,60 \pm 0,1$	0.444 ^c	
BMI (Kg/m ²)	34 (27.9–37.2)	32.9 ± 6.0	32.2 ± 4.4	0.590 ^c	
NC (cm)	40 (38–43)	40 (38–44)	41 (38–42.5)	0.925 ^b	
Smoking	3 (5.2%)	2 (6.1%)	1 (4%)	0.605 ^d	
AHI	24.5 (13.5–37.3)	25 (10.5-38)	22 (15-35.5)	0.747 ^b	
Severity of OSA				0.980^{a}	
Mild	17 (29.3%)	10 (30.3%)	7 (28%)		
Moderate	18 (31%)	10 (30.3%)	8 (32%)		
Severe	23 (39.7%)	13 (39.4%)	10 (40%)		
Use of CPAP	14 (24.1%)	9 (27.3%)	5 (20%)	0.522 ^a	
Severity of dysphagia				0.175 ^a	
Mild	41 (70.7%)	21 (63.6%)	20 (80%)		
Mild to moderate	17 (29.3%)	12 (36.4%)	5 (20%)		

p value for bivariate comparisons between groups completed and not complete of study

Values are presented as relative and absolute frequencies, mean \pm standard deviation, or medians (interquartile range)

BMI body mass index, *NC* neck circumference, *AHI* apnea–hypopnea index, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure

^aPearson's chi-square test

^bMann–Whitney test

^cIndependent samples test

^dFisher's exact test

Table 2Changes detected in thefiberoptic endoscopic evaluationof swallowing before and afterthe intervention

Changes of the FEES	Before intervention	After intervention	p value
Premature spillage			0.508^{a}
Yes	26 (78.8%)	23 (69.7%)	
No	7 (21.2%)	10 (30.3%)	
Number of swallows	2 (1-3)	3 (2–4)	0.001 ^b
Delay of the pharyngeal phase			0.035 ^a
Yes	27 (81.9%)	18 (54.6%)	
No	6 (18.1%)	15 (45.4%)	
Onset of the pharyngeal phase	2 (2–2)	1 (1–1)	0.001 ^b
Penetration-aspiration			0.001 ^a
Yes	18 (54.6%)	5 (15.2%)	
No	15 (45.4%)	28 (84.8%)	
Level of penetration-aspiration	3 (2–4)	2 (2–2)	0.007 ^b
Pharyngeal residue			0.001 ^a
Yes	26 (78.8%)	7 (21.2%)	
No	7 (21.2%)	26 (78.8%)	
Degree of pharyngeal residue	2 (2–2.5)	1 (0–1)	0.001 ^b
Severity of dysphagia	5 (4–5)	6 (5–6)	0.001 ^b

Values are presented as relative and absolute frequencies, mean±standard deviation, or medians (interquartile range)

^aMcNemar chi-square test

^bWilcoxon signed-rank test

penetration-aspiration (k=0.93), and penetration-aspiration level (k=0.81).

Table 3 shows the association between the anthropometric and clinical characteristics of the participants and the FEES outcome. The individuals who improved the level of penetration–aspiration were younger and female. Women also showed improvement in the degree of pharyngeal residue. The improvement of dysphagia occurred mainly among the participants with a lower AHI.

Although not statistically significant, it was observed that most individuals who did not show improvement in the level of penetration–aspiration or in the degree of pharyngeal residue after the intervention had higher AHI, more often had severe OSA, and more often used CPAP. In addition, the group that did not show improvement in the degree of pharyngeal residue was older than the group that showed improvement, again without statistical significance.

Figure 2 shows how the degree of oropharyngeal dysphagia changed from before to after the swallowing therapy program. Of the 33 individuals with oropharyngeal dysphagia, 26 (78.8%) exhibited improvement in the degree of oropharyngeal dysphagia, 6 (18.2%) stayed the same, and 1 (4.8%) exhibited worsening oropharyngeal dysphagia after the intervention. There was a statistically significant difference in the degree of dysphagia between the time before and after the intervention (p < 0.001). Regarding the 21 (100%) individuals diagnosed with mild dysphagia before the intervention, after therapy program, 1 (4.8%) evolved to normal swallowing, 14 (66.7%) to functional swallowing, 5 (23.8%) still had mild dysphagia, and 1 (4.8%) presented functional worsening with progression to mild to moderate dysphagia. Among the 12 (100%) patients with mild to moderate dysphagia before the intervention, after therapy program, 8 (66.7%) progressed to functional swallowing, 3 (25%) progressed to mild dysphagia, and 1 (8.3%) maintained a mild to moderate degree of dysphagia.

The total EAT-10 score (p = 0.023) was significantly lower after the swallowing therapy program [2 (0-6) vs. 0](0-3)], as was item 8 of the instrument (p = 0.002) [1 (0-4) vs. 0(0-3)]. The medians of the other EAT-10 items were equal to zero before and after de the swallowing therapy program (p > 0.05). Regarding the domains of the EAT-10, the medians before and after the swallowing therapy program, respectively, were 0 (0-1) and 0 (0-0) for the functional domain (p = 0.323); 0 (0–0) and 0 (0–0) for the emotional domain (p=0.590); and 2 (0-5) and 0 (0-2) for the physical domain (p = 0.008). There was no significant difference in the score of the functional or emotional domain from before to after the therapy program. However, the EAT-10 physical domains score was significantly lower after the intervention than before (p=0.008). The comparison between frequency of the scores obtained on each item of the EAT-10 before and after the swallowing therapy program showed that there was an increase in the frequency of the 0 score (absence of symptoms) on all items of the EAT-10 instrument after the

European	Archives o	f Oto-Rhino-l	Laryngology
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Table 3 Association between the anthropometric and clinical characteristics of the participants and the FEES outcome

Outcome	Age	AHI	BMI	Male sex	Smoking	Use of CPAP	Severity of OSA		
							Mild	Moderate	Severe
Premature spillage									
Improvement $(n=10)$	65.5 (61.5–67)	16.5 (7.8–37.3)	31.2±5.8	3 (30%)	0 (0%)	4 (40%)	5 (50%)	1 (10%)	4 (40%)
Worsened $(n=23)$	64 (58–67)	28 (16-38)	33.7±6.1	7 (30.4%)	2 (8.7%)	5 (21.7%)	5 (21.7%)	9 (39.1%)	9 (39.1%)
<i>p</i> value	0.491 ^a	0.378 ^a	0.288 ^b	0.657 ^c	0.479 ^c	0.252 ^c	0.138 ^c		
Delay of the PP									
Improvement $(n=15)$	64 (59–67)	29 (8-38)	32.7 ± 6.5	6 (40%)	1 (6.7%)	3 (20%)	6 (40%)	2 (13.3%)	7 (46.7%)
Worsened $(n = 18)$	64.5 (58.8-66.3)	25 (15.5–34.8)	33.1 ± 5.8	4 (22.2%)	1 (5.6%)	6 (33.3%)	4 (22.2%)	8 (44.4%)	6 (33.3%)
<i>p</i> value	0.928 ^a	0.844 ^a	0.844 ^b	0.234 ^c	0.710 ^c	0.324 ^c	0.174 ^c		
Level of P-A									
Improvement $(n=28)$	63 (58.3–66)	22 (9.8–36.3)	33.4±6.1	6 (21.4%)	1 (3.6%)	6 (21.4%)	9 (32.1%)	10 (35.7%)	9 (32.1%)
Worsened $(n=5)$	67 (65.5–67)	50 (20-77)	30.0 ± 4.9	4 (80%)	1 (20%)	3 (60%)	1 (20%)	0 (0%)	4 (80%)
p value	0.018 ^a	0.108 ^a	0.243 ^b	0.021 ^c	0.284 ^c	0.111 ^c	0.154 ^c		
Pharyngeal residue									
Improvement $(n=26)$	63.5 (58–66.3)	22 (8–37.25)	33.5 ± 6.1	5 (19.2%)	1 (3.8%)	5 (19.2%)	9 (34.6%)	9 (34.6%)	8 (30.8%)
Worsened $(n=7)$	66 (63–68)	34 (16–59)	30.8 ± 5.5	5 (71.4%)	1 (14.3%)	4 (57.1%)	1 (14.3%)	1 (14.3%)	5 (71.4%)
<i>p</i> value	0.111 ^a	0.090 ^a	0.310 ^b	0.016 ^c	0.384 ^c	0.068 ^c	0.235 ^c		
Number of swallows									
Improvement $(n=23)$	63 (59–66)	19 (8–37)	32.8 ± 5.8	5 (21.7%)	1 (4.3%)	4 (17.4%)	8 (34.8%)	7 (30,4%)	8 (34,8%)
Worsened $(n = 10)$	65,5 (61–68)	29 (15.8–64)	33.2 ± 6.9	5 (50%)	1 (10%)	5 (50%)	2 (20%)	3 (30%)	5 (50%)
<i>p</i> value	0.168 ^a	0.176 ^a	0.849 ^b	0.114 ^c	0.521 ^c	0.068 ^c	0.733 ^c		
Severity of dysphagia									
Improvement $(n=26)$	64 (59–66.3)	19 (8–34.8)	33.1 ± 6.0	6 (23.1%)	1 (3.8%)	6 (23.1%)	9 (34.6%)	9 (34.6%)	8 (30.8%)
Worsened $(n=7)$	65 (58–68)	38 (28–59)	32.2 ± 6.6	4 (57.1%)	1 (14.3%)	3 (42.9%)	1 (14.3%)	1 (14.3%)	5 (71.4%)
p value	0.465 ^a	0.034 ^a	0.730 ^b	0.103 ^c	0.384 ^c	0.277 ^c	0.235 ^c		

Statistical significance values are shown in bold

Improvement = individuals who showed improvement or remained unchanged after the intervention; Worsened = who exhibited worsening or remained with alterations after the intervention. *AHI* apnea–hypopnea index, *BMI* body mass index, *CPAP* continuous positive airway pressure, *OSA* obstructive sleep apnea, *PP* pharyngeal phase, *P–A* penetration–aspiration

Values are presented as relative and absolute frequencies, mean \pm standard deviation, or medians (interquartile range). p value for bivariate comparisons between groups improvement and worsened

^aMann-Whitney test

^bIndependent samples test

°Fisher's exact test

swallowing therapy program. Items 8 and 9 were the ones that most scored > 0, indicating a higher frequency of symptoms related to food stuck/stuck in the throat and coughing when eating.

Regarding the Swal–QoL, the sleep domain was the one that most affected the quality of life, and it showed no improvement after the intervention [50 (50–50) before and after the intervention, p = 0.754]. The score for the symptom frequency domain was significantly higher after the intervention

than before the therapy program [92.8 (75–100) vs. 98.2 (87.5–100), p = 0.002]. The scores of the other domains did not change after the intervention (p > 0.05). The medians of the Swal–QoL domains before and after intervention were, respectively: general burden [100 (87.5–100) vs. 100 (75–100)], eating desire [91.6 (75–100) vs. 100 (83.3–100)], eating duration [100 (37.5–100) vs. 100 (37.5–100)], food selection [100 (81–100) vs. 100 (93.7–100)], communication [100 (93.7–100) vs. 100 (100–100)], fear for eating [100 (59.3–100)



Fig. 2 Degree of oropharyngeal dysphagia changed from before to after the swallowing therapy program. Marginal homogeneity: p < 0.001. Degree of dysphagia oropharyngeal: (1) severe dysphagia, (2) moderate to severe dysphagia; (3) moderate dysphagia; (4) mild to moderate dysphagia; (5) mild dysphagia; (6) functional swallowing; and (7) normal swallowing. Dysphagia was considered present with a score < 6

vs. 100 (81.2–100)], mental health [100 (100–100) vs. 100 (100–100)], social effects [100 (100–100) vs. 100 (100–100)], fatigue [91.6 (54.1–100) vs. 83.3 (50–100)].

Discussion

Our study is the first one to demonstrate that resistant hypertensive patients diagnosed with oropharyngeal dysphagia secondary to OSA submitted to a swallowing therapy program show improved swallowing performance. The outcomes of the therapy program indicate not only the improvement of swallowing biomechanics but also the selfperception of dysphagia symptoms and the individual's quality of life. Although scientific evidence has positioned orofacial myofunctional therapy as a conservative therapeutic proposal for the treatment of OSA, no previous studies have addressed swallowing therapy program for the rehabilitation of oropharyngeal dysphagia in individuals with OSA.

Fiberoptic endoscopic evaluation of swallowing (FESS)

The present study showed that resistant hypertensive individuals diagnosed with OSA and oropharyngeal dysphagia who underwent swallowing therapy program had an increase in the number of swallows and improvement of the degree of oropharyngeal dysphagia, level of penetration–aspiration, degree of pharyngeal residue, scale of pharyngeal residue, and scale of onset of the pharyngeal phase. After therapy program, most individuals reached a level of laryngeal penetration considered physiological [23] and no longer exhibited pharyngeal residue (absent degree or trace) (Table 2).

Most individuals exhibited onset of the pharyngeal phase in the pyriform sinuses, a phenomenon frequently observed in elderly subjects with comorbidities who are at risk for dysphagia [21], before the intervention and began to exhibit the onset of the pharyngeal phase in the vallecula afterward. It is noteworthy that unlike the severity of dysphagia, the degree of pharyngeal residue, and the level of penetration-aspiration presented by the participants before the swallowing therapy program, which indicated changes in swallowing, the onset of the pharyngeal phase in pyriform sinuses swallowing disorder did not. However, the progression to the onset of the pharyngeal phase in the vallecula is favorable, as studies indicate that individuals with OSA have a longer latency time and need a greater volume of liquid to initiate the pharyngeal phase of swallowing, possibly due to sensory changes in the pharynx caused by snoring, intermittent hypoxia, and inflammatory processes [12]. The impairment of the upper airway neuromuscular afference present in patients with OSA and primary snorers compromises the central integration between swallowing and breathing functions, swallowing reflex, and thus the oropharyngeal mechanics and swallowing dynamics [6-8].

The findings regarding the improvement of the scale at the beginning of the pharyngeal phase may suggest an improvement in the speed of the swallowing motor response of these individuals after the swallowing therapy program. In addition, both the findings related to the improvement of the scale of onset of the pharyngeal phase and the increase in the number of swallows may suggest improvement of pharyngeal sensitivity in these individuals after the therapy program (Table 2), even allowing adequate management in the case of pharvngeal residue. Thus, it is possible that the increase in the number of swallows contributed to the reduction of the degree of pharyngeal residue evidenced in the participants of this study. However, we cannot rule out the possibility of improvement of pharyngeal residue, as well as the level of penetration-aspiration, due to the improvement of the biomechanics of swallowing that came from the motor stimulation provided by the therapeutic program the participants undertook. This is because this program consisted of strategies that promote increased pharyngeal contraction [28], reduced pharyngeal transit time [29], and increased suprahyoid muscle activity, which is responsible for the elevation and anteriorization of the hyolaryngeal complex and opening of the pharyngoesophageal transition [30, 31].

Our results showed an association of male sex with no improvement of the degree of pharyngeal residue or the level of penetration-aspiration (Table 3). The relationship between sex and swallowing physiology is not fully understood, though studies indicate a greater pharyngeal muscle reserve and flexibility in the compensatory mechanism of swallowing more efficiently in women than in men [32]. In one study, the average duration of laryngeal closure was significantly longer in women than in men, and the onset of laryngeal closure occurred significantly earlier in women [33]. Another study indicated that women exhibit longer swallowing apnea than men, as well as longer duration of the pharyngeal phase and closing of the lower airway, which reduces the likelihood of penetration-aspiration events [34]. Considering the distance of the hyoid excursion displacement during deglutition, some researchers concluded that the hyoid displacement is greater in men than in women [35]. This reveals that the action of the suprahyoid muscles needs to be more efficient in men, given the greater area of anterior and superior displacement to be covered by the hyoid to provide closure of the laryngeal atrium and opening of the pharyngoesophageal transition [35]. Another aspect that could explain the differences observed between men and women concerns the social roles played by them, such as compliance with treatment, commitment to the correct execution of the proposed tasks, social behavior or habits during eating, rhythm control, and volume of oral intake, for example. The oropharyngeal transit is longer in women than in men for a 5-ml bolus, suggesting that women ingest liquids with a lower flow rate and lower volumes in each swallow than men [36]. However, it is noteworthy that all male participants in this study had severe OSA, whereas 43.5% of the women had mild OSA, 43.5% had moderate OSA, and 13% had severe OSA (p = 0.001). Therefore, the outcomes of no improvement of the level of penetration-aspiration and pharyngeal residue associated with male sex may also be influenced by the severity of OSA.

Regarding the severity of OSA alone, a higher AHI was associated with no improvement of the degree of dysphagia (Table 3). Lower OSA severity implies less impairment of the upper airway neuromuscular afference and central integration between swallowing and breathing functions. Thus, a lower AHI would correspond to better results in rehabilitation, with favorable clinical outcomes. Researchers have found that the greater the degree of severity of apnea, the greater the degree of impairment of orofacial structures [37]. Accordingly, our results showed a trend, albeit without statistical significance, that individuals who did not show improvement in the degree of pharyngeal residue after swallowing therapy program exhibited higher AHI and higher likelihood of using CPAP.

This study also revealed that there is an association between older age and the outcome of no improvement in the level of penetration–aspiration. The group that did not improve the level of penetration–aspiration after the swallowing therapy program was older than the group that did improve (Table 3). This finding is in line with the literature, which postulates that there is a greater predisposition to penetration–aspiration in older subjects [38]. The aging process changes the composition of the muscles, changing their shape and function and decreasing their contraction force [39]. These changes may compromise the efficiency of the pharyngeal mechanisms responsible for the conduction of the food bolus and protection of the lower airway [40], which could translate into a higher risk of penetration–aspiration. In this study, the median age was high, so the possibility of presbyphagia may have contributed to this result. Since age is also a risk factor for swallowing [41], early diagnosis and treatment is essential to providing more promising results.

In contrast, there was no significant reduction in the frequency of premature spillage after swallowing therapy program. A possible explanation for this result is that this signal is related to the modification of the oral phase of swallowing, and the therapeutic strategies applied in the therapy program of this study are directed to pharyngeal dynamics, since the changes in swallowing present in these individuals are caused by neurogenic lesions in the pharynx [14, 15].

Eating Assessment Tool (EAT-10)

Our results indicate a reduction in the frequency and severity of dysphagia symptoms after swallowing therapy program. Only the symptoms "When I swallow, food sticks in my throat" and the physical domain showed statistically significant improvements after the therapy program. These were the only that exhibited a score greater than 0 before the intervention. This result agrees with the FEES findings revealed in this study regarding pharyngeal residue, identified by the participants as "food sticks in my throat".

Swallowing-related quality of life (Swal–QoL)

In accordance with the literature, the present study showed that the sleep domain was the most affected in dysphagic individuals with OSA [7, 10]. This may be explained by the fact that individuals with OSA most often have symptoms impair sleep quality [42]. Although the literature indicates the benefit of speech therapy intervention for the treatment of OSA and improvement of sleep quality in individuals with OSA [19], this study found no improvement in the sleep domain after therapy program. This is because the swallowing therapy program applied to the participants of this study was directed to the rehabilitation of swallowing and not to the treatment of OSA. In contrast, our results showed a statistically significant improvement in the symptom frequency domain after the therapy program, which corroborates the improvement of dysphagia symptoms evaluated using the dysphagia risk assessment instrument.

This study has some limitations, including the absence of a control group to evaluate the efficacy of the swallowing therapy program for the treatment of oropharyngeal dysphagia in this population. Thus, although the design of this study does not allow us to conclude that the improvement of swallowing function observed in the study participants was due to the therapy program, it is noteworthy that, according to the literature, the neural lesions in the pharynx, identified as responsible for the changes in swallowing in individuals with OSA, are progressive [13, 14, 43]. Therefore, a spontaneous recovery of the swallowing dynamics of these individuals would not be expected. Other limitations are related to the sample size, as it was not possible to increase the number of participants due to the suspension of the evaluation process for safety reasons due to COVID-19. FEES is limited in its evaluation of the oral phase of swallowing, and the follow-up time of the study was short. Since the participants were evaluated only at two time points, before and after 8 weeks of intervention, it is not possible to guarantee that the improvement of swallowing efficiency and safety observed here will be maintained in the medium and long term.

Conclusions

Resistant hypertensive patients with OSA and oropharyngeal dysphagia showed improved swallowing safety and efficiency, lower risk of dysphagia, and higher quality of life during swallowing after the swallowing therapy program. Younger female patients with lower AHI had a better swallowing response to the therapy program.

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Data availability Available.

Code availability Available.

Declarations

Conflict of interest The authors declare that they do not have any conflict of interest.

Ethical approval The study was approved by the research ethics committee of Hospital Universitário Clementino Fraga Filho (HUCFF): number 2.213.968.

Informed consent Participation in the study was voluntary, and all participants signed the informed consent form (ICF).

References

- Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR et al (2018) Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 72(5):e53-90. https://doi.org/10.1161/HYP.00000000000084
- Üksel A, Kulan CA, Bilgin RR, Ünsal YO, Yurtman N et al (2019) Examination of the relationship of asymptomatic swallowing disorder prevalence with hypertension, diabetes and obesity in elderly population. J Geriatr Med Gerontol 5:071. https://doi.org/ 10.23937/2469-5858/1510071
- Muxfeldt ES, Margallo VS, Guimarães GM, Salles GF (2014) Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. Am J Hypertens 27(8):1069– 1078. https://doi.org/10.1093/ajh/hpu023
- Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults obstructive sleep apnea task force of the American Academy of Sleep Medicine. J Clin Sleep Med 5(3):263–276
- Bhutada AM, Broughton WA, Focht Garand KL (2020) Obstructive sleep apnea syndrome (OSAS) and swallowing function-a systematic review. Sleep Breath 24(3):791–799. https://doi.org/ 10.1007/s11325-020-02037-w
- Valbuza JS, de Oliveira MM, Zancanella E, Conti CF, Prado LB, Carvalho LB, do Prado GF (2011) Swallowing dysfunction related to obstructive sleep apnea: a nasal fibroscopy pilot study. Sleep Breath 15(2):209–213. https://doi.org/10.1007/ s11325-010-0474-9
- Schindler A, Mozzanica F, Sonzini G, Plebani D, Urbani E, Pecis M, Montano N (2014) Oropharyngeal dysphagia in patients with obstructive sleep apnea syndrome. Dysphagia 29(1):44–51. https://doi.org/10.1007/s00455-013-9474-9
- Oliveira LA, Fontes LH, Cahali MB (2015) Swallowing and pharyngo-esophageal manometry in obstructive sleep apnea. Braz J Otorhinolaryngol 81(3):294–300. https://doi.org/10.1016/j.bjorl. 2015.03.006
- Campanholo MAT, Caparroz FA, Stefanini R, Haddad L, Bittencourt LRA, Tufik S, Haddad FLM (2021) Dysphagia in patients with moderate and severe obstructive sleep apnea. Braz J Otorhinolaryngol 87(4):422–427. https://doi.org/10.1016/j.bjorl.2019. 10.004
- Caparroz FA, de AlmeidaTorresCampanholo M, Sguillar DA, Haddad L, Park SW, Bittencourt L, Tufik S, Haddad FLM (2019) A pilot study on the efficacy of continuous positive airway pressure on the manifestations of dysphagia in patients with obstructive sleep apnea. Dysphagia 34(3):333–340. https://doi.org/10. 1007/s00455-018-9944-1
- 11. Brendim MP, Muniz CR, Borges TGV, Ferreira FR, Muxfeldt ES (2022) Fiberoptic endoscopic evaluation of swallowing and the Brazilian version of the Eating Assessment Tool-10 in resistant hypertensive patients with obstructive sleep apnea. Braz J Otorhinolaryngol. https://doi.org/10.1016/j.bjorl.2022.01.006
- Teramoto S, Sudo E, Matsuse T, Ohga E, Ishii T, Ouchi Y, Fukuchi Y (1999) Impaired swallowing reflex in patients with obstructive sleep apnea syndrome. Chest 116:17–21. https://doi.org/10. 1378/chest.116.1.17
- Teramoto S, Ishii T, Matsuse T (2001) Relationship between swallowing function and gas exchange during day and night in patients with obstructive sleep apnea syndrome. Dysphagia 16(4):249– 253. https://doi.org/10.1007/s00455-001-0083-7
- 14. Friberg D, Gazelius B, Hökfelt T, Nordlander B (1997) Abnormal afferent nerve endings in the soft palatal mucosa of sleep apnoics

and habitual snorers. Regul Pept 71(1):29–36. https://doi.org/10. 1016/S0167-0115(97)01016-1

- Shah F, Forsgren S, Holmlund T, LevringJäghagen E, Berggren D, Franklin KA, Stål P (2018) Neurotrophic factor BDNF is upregulated in soft palate muscles of snorers and sleep apnea patients. Laryngoscope Investig Otolaryngol 4(1):174–180. https://doi.org/ 10.1002/lio2.225
- de Luccas GR, Berretin-Felix G (2021) Swallowing disorders in patients with obstructive sleep apnea: a critical literature review. Sleep Sci. 14(Spec 1):79–85. https://doi.org/10.5935/1984-0063. 20200034
- Pizzorni N, Radovanovic D, Pecis M, Lorusso R, Annoni F, Bartorelli A, Rizzi M, Schindler A, Santus P (2021) Dysphagia symptoms in obstructive sleep apnea: prevalence and clinical correlates. Respir Res 22(1):117. https://doi.org/10.1186/ s12931-021-01702-2
- Ferreira FR, Borges TGV, Muniz CR, Brendim MP, Muxfeldt ES (2021) Fiberoptic endoscopic evaluation of swallowing in resistant hypertensive patients with and without sleep obstructive apnea. Dysphagia. https://doi.org/10.1007/s00455-021-10380-7
- Kayamori F, Bianchini EMG (2017) Effects of orofacial myofunctional therapy on the symptoms and physiological parameters of sleep breathing disorders in adults: a systematic review. Revista CEFAC 19(6):868–878. https://doi.org/10.1590/1982-02162 01719613317
- Baijens LW, Pilz W, Kremer B, Passos VL (2015) Identifying patterns of FEES-derived swallowing trajectories using group-based trajectory model. Dysphagia 30(5):529–539. https://doi.org/10. 1007/s00455-015-9632-3
- Zancan M, Luchesi KF, Mituuti CT, Furkim AM (2017) Locais de início da fase deglutição: meta-análise. CoDAS 29(2):e20160067. https://doi.org/10.1590/2317-1782/20172016067
- Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL (1996) A penetration aspiration scale. Dysphagia 11:93–98. https://doi. org/10.1007/BF00417897
- Steele CM, Grace-Martin K (2017) Reflections on clinical and statistical use of the penetration aspiration scale. Dysphagia 32(5):601–616. https://doi.org/10.1007/s00455-017-9809-z
- Neubauer PD, Rademaker AW, Leder SB (2015) The Yale pharyngeal residue severity rating scale: an anatomically defined and image-based tool. Dysphagia 30(5):521–528. https://doi.org/10. 1007/s00455-015-9631-4
- O'Neil KH, Purdy M, Falk J, Gallo L (1999) The dysphagia outcome and severity scale. Dysphagia 14(3):139–145. https://doi. org/10.1007/PL00009595
- Gonçalves MIR, Remaili CB, Behlau M (2013) Equivalência cultural da versão brasileira do eating assessment Tool—EAT-10. CoDAS 25(6):2–5. https://doi.org/10.1590/S2317-17822013. 05000012
- Bandeira AK, Azevedo EH, Vartanian JG, Nishimoto IN, Kowalski LP, Carrara-de AE (2008) Quality of life related to swallowing after tongue cancer treatment. Dysphagia 23(2):183–192. https:// doi.org/10.1007/s00455-007-9124-1
- Aoyagi Y, Ohashi M, Ando S, Inamoto Y, Aihara K, Matsuura Y, Imaeda S, Saitoh E (2021) Efect of tongue-hold swallow on pharyngeal contractile properties in healthy individuals. Dysphagia 36:936–943. https://doi.org/10.1007/s00455-020-10217-9
- Machado JRS, Steidl EMS, Bilheri DFD, Trindade M, Weis GL, Jesus PRO, Pereira MB, Mancopes R (2015) Efeitos do exercício muscular respiratório na biomecânica da deglutição de indivíduos normais. Rev CEFAC 17(6):1909–1915. https://doi.org/10.1590/ 1982-0216201517621514
- Sze WP, Yoon WL, Escoffier N, Rickard Liow SJ (2016) Evaluating the training effects of two swallowing rehabilitation therapies

using surface electromyography-chin tuck against resistance (CTAR) Exercise and the Shaker Exercise. Dysphagia 31(2):195–205. https://doi.org/10.1007/s00455-015-9678-2

- Park JS, Hwang NK (2021) Chin tuck against resistance exercise for dysphagia rehabilitation: a systematic review. J Oral Rehabil 48(8):968–977. https://doi.org/10.1111/joor.13181
- Logemann JA, Pauloski BR, Rademaker AW, Kahrilas PJ (2002) Oropharyngeal swallow in younger and older women: videofluoroscopic analysis. J Speech Lang Hear Res 45:434–445. https://doi. org/10.1044/1092-4388(2002/034)
- Kurosu A, Logemann JA (2010) Gender effects on airway closure in normal subjects. Dysphagia 25(4):284–290. https://doi.org/10. 1007/s00455-009-9257-5
- 34. Hiss SG, Treole K, Stuart A (2001) Effects of age, gender, bolus volume, and trial on swallowing apnea duration and swallow/ respiratory phase relationships of normal adults. Dysphagia 16(2):128–135. https://doi.org/10.1007/s004550011001
- Molfenter SM, Steele CM (2014) Use of an anatomical scalar to control for sex-based size differences in measures of hyoid excursion during swallowing. J Speech Lang Hear Res 57(3):768–778. https://doi.org/10.1044/2014_JSLHR-S-13-0152
- Dantas RO, Aguiar CR, Santos CM et al (2009) Effect of gender on swallow event duration assessed by videofluoroscopy. Dysphagia 24:280–284. https://doi.org/10.1007/s00455-008-9202-z
- de Miranda VSG, Buffon G, Vidor DCGM (2019) Perfil miofuncional orofacial de pacientes com distúrbios do sono: relação com resultado da polissonografia. CoDAS. https://doi.org/10.1590/ 2317-1782/20182018183
- Daggett A, Logemann J, Rademaker A, Pauloski B (2006) Laryngeal penetration during deglutition in normal subjects of various ages. Dysphagia 21(4):270–274. https://doi.org/10.1007/ s00455-006-9051-6
- Leite LEA, Resende TL, Nogueira GM, Cruz IBM, Schneider RH, Gottlieb MGV (2012) Envelhecimento, estresse oxidativo e sarcopenia: uma abordagem sistêmica. Rev Brasil Geriatr Gerontol 15(2):365–380. https://doi.org/10.1590/S1809-982320120002000 18
- 40. Wirth R, Dziewas R, Beck AM, Clavé P, Hamdy S, Heppner HJ et al (2016) Oropharyngeal dysphagia in older persons - from pathophysiology to adequate intervention: a review and summary of an international expert meeting. Clin Interv Aging 11:189–208. https://doi.org/10.1590/S1809-98232012000200018
- Robbins JA (1999) Old swallowing and dysphagia: thoughts on intervention and prevention. Nutr Clin Pract 14:21–26. https://doi. org/10.1177/0884533699014005S05
- Bulcun E, Ekici A, Ekici M (2012) Quality of life and metabolic disorders in patients with obstructive sleep apnea. Clin Invest Med 35(2):105–113. https://doi.org/10.25011/cim.v35i2.16294
- Patel JA, Ray BJ, Fernandez-Salvador C, Gouveia C, Zaghi S, Camacho M (2018) Neuromuscular function of the soft palate and uvula in snoring and obstructive sleep apnea: a systematic review. Am J Otolaryngol 39(3):327–337. https://doi.org/10. 1016/j.amjoto.2018.03.006

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