The Additive Effectiveness of Inspiratory Muscle Training on Glottic Closure and Subjective Voice Outcomes of Patients With Benign Lesion After Hyaluronic Acid Laryngoplasty

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Abstract: Objectives. For patients with glottic insufficiency disease, injection laryngoplasty is a rapid and efficient management option that complements voice therapy. Some studies have indicated that respiratory muscle training may also show promise in patients with voice disorders. However, the effect of respiratory muscle training in patients with glottic insufficiency was reported to be limited, and whether it provides additional benefit after standard management requires further evaluation. We aimed to investigate the effectiveness of inspiratory muscle training on glottis closure and patient-reported voice quality in glottic insufficiency patients who had been treated with hyaluronic acid injection.

Study Design. Retrospective observational study.

Methods. We included 46 patients with glottic insufficiency who had undergone hyaluronic acid injection. Twenty of them had undergone inspiratory muscle training during three months. We measured patients' changes in glottic status according to the normalized glottal gap area and bowing index, as well as voice quality of life according to the voice handicap index 10 and the voice outcome survey, before and after training.

Results. Patients who underwent inspiratory muscle training had higher odds of experiencing better improvement in all scores. The range of odds ratios ranged from 2.5 to 6.3 for changes in scores, and from 3.8 to 22.2 for changes in score percentages. Of note, the effect of training on percentage changes in the normalized glottal gap area score was significant (P= 0.0127) after adjustment for the duration of vocal disease, body mass index and BMI, and history of gastroesophageal reflux disease.

Conclusions. Inspiratory muscle training can improve the glottal gap after injection laryngoplasty, and may be applied in clinical practice.

Key Words: Glottic insufficiency−Vocal cords−Phonation−Vocal fold paralysis−Hyaluronic acid−Respiratory muscle training.

Abbreviations: BI, bowing index−CAPE-V, consensus auditory-perceptual evaluation of voice−EMT, expiratory muscle training−GERD, gastroesophageal reflux disease−GRBAS, grade, roughness, breathiness, asthenia, and strain−HA, hyaluronic acid−IA, injection augmentation−IMT, inspiratory muscle training−IQR, interquartile range−MEP, maximal inspiratory pressure−NGGA, normalized glottal gap area−PEF, peak expiratory flow−QOL, quality of life−RMT, respiratory muscle training−VHI-10, Voice Handicap Index 10−VOS, voice outcome survey.

INTRODUCTION

During the lst few decades, there has been increasing interest in voice disorders, and glottic insufficiency is one of the causes of voice disorders.[1,2] Patients with glottic insufficiency have incomplete vocal cord closure. As the voice is produced by generating mucosal wave movements of the vocal folds by contacting and vibrating,[3-5] incomplete contact of the vocal cords will hamper vocal function. Furthermore, the leakage of air through the incomplete closure of the vocal cord makes it more difficult to increase and maintain the pressure in the airway during phonation, resulting in breathiness, weak voice, and easily fatigued patients.[4] In addition, aspiration is a common symptom in these patients.[6] Potential causes of glottic insufficiency include vocal fold paralysis, vocal fold paresis, presbylaryngitis, sulcus vocalis, vocal fold nodules, and neoplasm.[4,7,8]

Restoration of glottic competence may improve voice quality and reduce aspiration risk. Several treatments are available for glottic insufficiency. One treatment option is injection augmentation (IA). Various materials such as collagen,[9,10] hyaluronic acid (HA),[11] and autologous fat[12] have been used for injection. HA is a naturally occurring biocompatible polysaccharide without tissue specificity or immunogenicity and is widely used. Its strong hydrophilic

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and hygroscopic properties are suitable for the volume augmentation of tissue.[13] However, the effect of HA injections is not permanent.[13] The commonly used commercially available HA for temporary vocal fold injection has expected clinical longevity of 3 to 6 months.[13-15]

In addition to the relatively invasive treatments, there are also some conservative treatments for patients with voice disorders. Clinically, it occurs more commonly in patients who undergo injection laryngoplasty followed by conservative voice therapy.[16,17] The duration of the injection laryngoplasty effect tended to be slightly longer in the patients who received postinjection voice therapy.[17] In recent years, respiratory muscle training (RMT) has become a choice for patients with voice disorder.[18-21] RMT was originally used to strengthen the respiratory muscles and improve respiratory function.[22-25] As the RMT was able to strengthen the patient's respiratory muscles, it could improve their maximum expiratory and inspiratory pressure, and the total airflow passed through the glottic.[23,26-28] Owing to these characteristics, RMTs have the ability to improve phonation. RMT includes inspiratory muscle training (IMT) and expiratory muscle training (EMT). EMT has been proven to be beneficial for vocal function in professional workers and patients with Parkinson's disease, and IMT has been shown to improve maximum phonation time and quality of life (QOL).[29,30] Increasing respiratory pressure and airflow may improve phonation in patients with glottic insufficiency. However, in patients with glottic insufficiency or other voice disorders, RMT has not been demonstrated to provide additional benefits to usual treatments (including injection augmentation or voice therapy).

In this study, we aimed to evaluate the effectiveness of RMT on glottic closure and patient-reported voice quality in patients with glottic insufficiency treated with a hyaluronic acid injection. We focused on exploring the effects of IMT, rather than EMT, because vocal cord abduction during inspiration will likely cause less HA consumption than increasing contact of the vocal cords resulting from frequent adduction during expiration.

MATERIALS AND METHODS

Design and study population

This retrospective cohort study included patients diagnosed with glottic insufficiency diseases and treated with HA injection laryngoplasty at the National Cheng Kung University Hospital in Taiwan between 2015 and 2022. Informed consent was obtained from all the participants at the outpatients department. Glottic insufficiency diseases include vocal cord palsy, atrophic vocal cords, sulcus vocalis, and incomplete glottic closure. Patients were further excluded if the disease was indicated by an excisional procedure, such as a tumor or vocal polyp, or if the patient lacked fiberscope images owing to contraindications or other reasons. To maintain analytical simplicity, we included the first record of a patient who had undergone repeated HA injection laryngoplasty during the study period.

The inspiratory muscle training program

The included patients were divided into two groups based on whether they had received IMT after HA injection. At our hospital, all patients with glottic insufficiency who underwent HA injection were asked at the first follow-up outpatient visit after HA injection, regardless of whether they would like to receive IMT. If the patients intended to participate in the training, they were referred to a respiratory therapist, who instructed them on a 3-month IMT protocol. An inspiratory threshold trainer (Bravo™ Trainer, GaleMed Corporation, Taiwan) was used in the protocol. In addition, the initial threshold was set at level 3 or 4 (corresponding to resistance pressures of 55mmH_2O and 71mmH_2Or, respectively). Using the threshold trainer's mouthpiece, participants were instructed to expire deeply and then forcefully inspire. Three sets of 5 minute training sessions per day were performed at least 5 days a week for 3 months, resulting in at least 60 sets of training per month or a total of 180 sets of training in 3 months. The patients attended the outpatient clinic and were followed up by the respiratory therapist two weeks, one month, and 3months after the protocol started. IMT was performed under supervision on the follow-up day and at home on all the other days.

Outcome measures

The primary outcomes of interest included the change in glottis closure measured using the normalized glottal gap area (NGGA)[31] scale and the bowing index (BI).[32] As glottic insufficiency was characterized by incomplete glottal closure, we used these two scales, which can both assess vocal cord status while phonating under the fiberscope, to assess glottic status. Fiberscope examinations before IMT (preoperatively) and after IMT (at the 3-month postoperative outpatient visit) were conducted. Each patient was video-recorded at a frame rate of 30 fps. Patients were asked to phonate /i/ in their regular speech tone and loudness. The glottic closure was analyzed on the frame in which the glottic gap was the narrowest during the patient's phonation

The National Greentown Glass Association, Inc. (NGGA) measures the glottic gap and is calculated using the formula (narrowest glottal-gap area/membranous vocal fold length) $\times$ 100. A lower NGGA value was more favorable because it indicated a smaller glottal gap during phonation. To quantify the vocal fold bowing, BI was calculated as W/L $\times$ 100, where "L" was the length of the vocal fold measured from the anterior commissure to the tip of the vocal process and "W" was the maximum distance from "L" to the vocal fold edge at the mid-membranous area. The BI assesses the bowing of the vocal cord, with a smaller value indicating better phonation. In this study, the BI value of every patient is presented as the average of the right and left BI. Both scales were calculated using the ImageJ software.[33] The stripe tool was used to mark the length, including the membranous vocal fold lengths W and L. A freehand selection tool was used to outline the glottic gap. The measure tool was used to calculate and express the results in pixels.

The secondary outcomes were subjective voice quality, including the Voice Handicap Index 10 (VHI-10)[34] and Voice Outcome Survey (VOS)[35] scores reported by patients before IMT (preoperatively) and after IMT (at the postoperative outpatient visit after 3 months). Validated Mandarin Chinese versions of both the scoring scales were used.[36,37] The VHI-10 included three subscales: functional, emotional, and physical. The functional subscale includes statements that describe the "impact of a person's voice disorders on his or her daily activities." The emotional subscale indicates the patient's "affective responses to a voice disorder." The items in the physical subscale are related to patients' self-perceptions of laryngeal discomfort and voice output characteristics. Each part of the questionnaire included 10 questions, and each question had 5-scale response (from 0 to 4). The scores were added, with lower scores indicating better voice quality of life. The VOS included five questions. The first question of the VOS concerned the global question of voice quality with a 5-scale response. Additional items were designed to evaluate patient limitations in certain daily activities that required speaking or limitations in their social or work-related activities because of vocal problems. There were five questions in total, and each question had a response with different scale. Lower VOS scores indicate a better voice outcome. Both scales were performed with the patient undergoing a fiberscope examination before the HA injection and again at the 3 months follow-up.

Other data collection

Patient data were collected from a review of the electronic medical records. These included sex, birth, cause of glottic insufficiency, diagnostic date of glottic insufficiency, injection site, surgery date, body mass index, the intensity of voice use,[38] educational background, smoking status,[39] ingestion of stimulants (habit of consuming coffee, tea, alcohol, iced drinks, or spicy food),[40] medical history of malignancy, cardiovascular disease, and gastroesophageal reflux disease(GERD).[41]

Statistical analyses

Categorical variables are presented as counts with percentages, while continuous variables are presented as medians with interquartile ranges (IQR). Patient characteristics, changes in NGGA, BI, VHI-10, VOS scores, and percentages were compared between the IMT-treated and non-IMT groups using a *t*-test and chi-square test (or Mann-Whitney *U* test and Fisher's exact test if the variable was not normally distributed). Given the limited sample size and non-normal distribution of some outcome variables, we applied the Wilcoxon signed-rank test to compare the changes in NGGA, BI, VHI-10, and VOS scores, and the percentages before and after HA injection were significantly different. Furthermore, we classified all included patients into high improvement and limited improvement groups for each outcome score. Those with score changes or percentile changes larger than the median values were classified as the high improvement group, while those with score changes or percentile changes less than the median values were classified as the limited improvement group. The median values of score changes and percentile changes in the included patients were -3.5/-35.8, -3.4/-35.9, -15.0/-51.3, and 27.8/100.0 for NGGA, BI, VHI-10, and VOS, respectively. We performed multivariable firth logistic regression to investigate the influence of IMT intervention on the odds of experiencing high improvement in different scores after adjusting for factors that were found to be significant between groups from previous univariate analyses. The significance level was set at $P < 0.05$. All analyses were conducted using Microsoft Excel and SAS software v9.4.

RESULTS

A total of 43 patients with vocal diseases who had undergone HA injections were included. Among them, 20 underwent IMT, while 23 did not. In addition, 55% in the first group and 65% in the second group were men. The median (IQR) age was 59.5 (48.5−70.0) and 58.0 (50.0−66.0) for the IMT and the non-IMT groups, respectively (Table 1). Most patients were diagnosed with vocal cord palsy, while only a few were diagnosed with incomplete closure and an atrophic vocal cord. The median diagnosis duration of vocal disease in the IMT group was 1.5 months, which was longer than in the non-IMT group (0.9 months). Most of the patients underwent left-sided HA injection surgery. The distribution of the different intensities of voice use between the groups was similar. Compared with the IMT group, the non-IMT group had a higher proportion of patients with GERD (61% vs. 5%) and a higher median BMI (24.2 vs. 22.2). Other characteristics are presented in Table 1.

In terms of glottis closure assessment, the median preHA NGGA scores were 10.5 and 14.5, and the BI scores were 8.8 and 10.5 for the IMT and the non-IMT groups, respectively (Table 2). For patient-reported outcomes, the mean preHA VHI-10 scores were 37.0 and 35.5, and the VOS scores were 22.2 and 33.3 for the IMT and the non-IMT groups, respectively. For both the IMT and the non-IMT groups, the NGGA, BI, and VHI-10 decreased after HA injection ($P < 0.05$ for all paired *t*-tests), while the VOS increased (a decrease in NGGA, BI, VHI-10 or VOS represents an improvement in the voice disorder). The mean score changes were -4.1 and -2.9 in NGGA, -2.7 and -3.8 in BI, -15.0 and -18.0 in VHI-10, and +27.8 and 30.6 in VOS for the IMT and the non-IMT groups, respectively. When presented in percentages of score changes, the NGGA score in the IMT group was significantly decreased by 48.6% when compared to a 26.8% decrease in the non-IMT group (P= 0.0385). The detailed values for the other comparisons are presented in Table 2. However, the values displayed in Table 2 did not yet include adjustments for potential confounders, and only reflect the results of the univariate analysis.

The results of the multivariate firth logistic regression are presented in Table 3. Covariates that were significantly different between the IMT and non-IMT groups from Table 1 were adjusted for in the multivariate regression model. As

TABLE 1.
Characteristics of Patients

	IMT Group		Gon-IMT Group		
	N or value	% or IQR	N or value	% or IQR	*P* value
N	20		23		
Age, in years (median, IQR)	59.5	(48.5, 70.0)	58.0	(50.0, 66.0)	0.7282
Male	11	55.0%	15	65.2%	0.6317
Diagnosis of vocal disease	NA	NA	NA	NA	0.5773
Incomplete closure	1	5.0%	4	17.4%	NA
Vocal cord palsy	17	85.0%	16	69.6%	NA
Atrophic vocal cord	2	10.0%	3	13.0%	NA
*Duration of vocal disease, in months (median, IQR)**	1.5	(0.9, 3.4)	0.9	(0.4, 1.4)	0.0443
Surgery	NA	NA	NA	NA	0.0863
Right side	0	0.0%	5	21.7%	NA
Left side	15	75.0%	12	52.2%	NA
Bilateral	5	25.0%	6	26.1%	NA
History of cancer	7	36.8%	9	39.1%	0.8792
History of cardiovascular disease	0	0.0%	2	8.7%	0.4925
Intensity of voice use†	NA	NA	NA	NA	1
High intensity	3	15.0%	4	17.4%	NA
medium intensity	3	15.0%	3	13.0%	NA
Low intensity	13	65.0%	16	69.6%	NA
Education level with a bachelor's degree	5	29.4%	6	33.3%	0.8028
Smoking	6	30.0%	9	40.9%	0.4612
Intake of stimulant food‡	5	25.0%	4	18.2%	0.7139
GERD	1	5.0%	14	60.9%	0.0001
BMI (median, IQR)	22.2	(19.8, 25.0)	24.2	(23.1, 26.4)	0.0415
IMT level					
Level 2	1	5%	NA	NA	NA
Level 3	12	60%	NA	NA	NA
Level 4	7	35%	NA	NA	NA
Maximum inspiratory pressure, cmH2O (median, IQR)	55	(55, 71)	NA	NA	NA

* Duration of vocal disease was calculated as the duration between diagnosis time and surgery time of the vocal disease.
† Intensity of voice use was classified according to patients' professions. Patients were grouped as high intensity voice use if they were singers, actors, teachers, lecturers, sales representatives, clergy, coaches and trainers, call center workers or barristers that relies heavily on voice use. Patients were grouped as medium intensity voice use if they were doctors, business executives or lawyers that require come tasks in voice. Patients were grouped as low intensity voice use if they were administrative workers, clerks or taking other jobs that requires minimal tasks in voice.
‡ Stimulant food included coffee, tea, alcohol, iced and spicy food.Abbreviations: BMI, body mass index; GERD, gastroesophageal reflux disease; IQR, interquartile range; SD, standard deviation

shown in Table 3, patients who underwent IMT had higher odds of experiencing better improvement in all scores except the VOS. The odds ratios ranged from 2.6 to 13.1 for changes in score percentages. Notably, the effect of IMT on percentage changes in NGGA score was significant (P= 0.0212) after adjustment for the duration of vocal disease, BMI, and GERD history. For the other scores, the IMT group showed a trend toward higher odds of experiencing greater improvement when compared with the non-IMT group; however, the comparisons were statistically non-significant.

DISCUSSION

In our study, IMT following HA injection laryngoplasty seemed to benefit patients with glottic insufficiency disease. Patients who underwent IMT showed a larger glottal gap improvement than those who underwent HA injection alone. The improvement in bowing of the vocal cords and patient-reported voice outcomes did not differ.

Few studies have discussed the influence of IMT on vocal cord outcome. Most of these studies focused on patients with upper airway obstruction diseases, such as paradoxical vocal fold movement disorder,[42,43] recurrent laryngeal papilloma,[44] and bilateral abductor vocal fold paralysis.[45] A previous study demonstrated that IMT could improve the maximal inspiratory pressure (MIP),[21,23] maximal inspiratory pressure (MEP),[21] peak expiratory flow (PEF), and functional capacity of the lung.[46] Another study indicated that IMT provided benefits for patients with exercise-induced laryngeal obstruction owing to its ability to improve the strength of the cricoarytenoid muscle and increase vocal cord adduction.[47] In the study, the authors decribed not only vocal fold abduction during inspiration, but also slight adduction during

TABLE 2.
Outcome Scores of Patients

	IMT Group		Non-IMT Goup		
	Median	IQR	Median	IQR	P Value†
N	20		23		
NGGA					
PreHA score	10.5	(7.9, 14.2)	14.5	(10.8, 20.5)	
PostHA score	5.9	(4.4, 7.7)	11.0	(5.7, 13.3)	
Score changes (post - pre)	-4.1	(-8.7, -2.4)	-2.9	(-9.9, -2.2)	0.5347
Percentage of score changes	-48.6	(-65.4, -26.9)	-26.8	(-44.0, -14.2)	0.0385
P for pre and post analysis*	<0.0001	NA	<0.0001	NA	NA
BI					
PreHA score	8.8	(5.3, 18.2)	10.5	(6.6, 14.3)	NA
PostHA score	5.3	(3.4, 7.6)	7.4	(4.7, 8.9)	NA
Score changes (post - pre)	-2.7	(-10.6, -1.2)	-3.8	(-6.0, -0.8)	0.7982
Percentage of score changes	-35.8	(-57.5, -21.7)	-35.9	(-58.6, -12.7)	0.4953
P for pre and post analysis*	<0.0001	NA	0.0001	NA	NA
VHI-10					
PreHA score	37.0	(26.0, 38.0)	35.5	(33.0, 37.0)	NA
PostHA score	19.0	(13.0, 32.0)	14.0	(7.0, 20.0)	NA
Score changes (post - pre)	-15.0	(-21.0, 0.0)	-18.0	(-24.0, -13.0)	0.1045
Percentage of score changes	-37.5	(-63.2, 0.0)	-55.2	(-77.4, -37.1)	0.0353
P for pre and post analysis*	0.0133	NA	<0.0001	NA	NA
VOS					
PreHA score	22.2	(16.7, 33.3)	33.3	(16.7, 50.0)	NA
PostHA score	44.4	(33.3, 61.1)	66.7	(55.6, 72.2)	NA
Score changes (post - pre)	27.8	(0.0, 38.9)	30.6	(16.7, 44.4)	0.2180
Percentage of score changes	116.7	(0.0, 233.3)	62.5	(33.3, 175.0)	0.6446
p for pre and post analysis*	0.0005		<0.0001		

* Wilcoxon signed-rank test was applied to test the difference in scores before and after HA injection.
† Mann-Whitney *U* Test was applied to detect difference between IMT and non-IMT groups.
Abbreviations: BI, bowing index; NGGA, normalized glottal gap area; VHI-10, voice handicap index-10; VOS, voice outcome survey.

expiration. However, there is limited evidence of the effect of IMT on the glottic structure.

In our study, we found that the IMT group had a smaller glottal gap during phonation in patients with vocal insufficiency compared to the non-IMT group. This could not simply be explained by the adduction of the vocal cords, as IMT was more related to the abduction of the vocal cords.[47] There are two potential explanations for the benefits of IMT in maintaining glottal closure. The first might be a decrease in the mean subglottal pressure. The vocal folds modulate airflow by adjusting their resistance to maintain adequate glottal airflow for phonation. As the subglottal pressure increases, an increase in vocal fold approximation and/or stiffness is required to maintain a consistent glottal airflow.[47] If the subglottal pressure is too strong, the vocal folds may not be able to maintain resistance against it. Glottal airflow is likely to be elevated, and an increase in the glottal gap is required. In patients with vocal insufficiency disease, the ability to resist subglottic pressure is decreased. In a study by Castillo et al,[48] IMT was shown to decrease the mean subglottic pressure but still increased the peak subglottic pressure in phonation. Training inspiratory muscles can promote good airflow control. The inspiratory muscles are engaged during the expiratory phase of speech to control expiratory pressure.[49] The subglottal pressure is stable and can be easily modulated by the vocal folds. With this improved capability for maintaining position, a small glottal opening and a relatively constant mean flow can be maintained against subglottal pressure by a proportional increase in vocal fold approximation alone, without extra vocal fold stiffening.[50,51] Therefore, the glottal gap decreases during phonation.

In our patients, who had received HA injection, training with IMT reduced vocal cord adduction during training, resulting in less over-friction and/or phonotrauma of the augmented vocal cord contact site. In addition, IMT could lead to decreased hyperfunction of the vocal cord with decreasing additional stiffness of the vocal cord on the approximation of the vocal cord owing to better control of the subglottic pressure.[50] Hyperfunction and phonotrauma of the vocal cords may increase inflammation and blood flow in the vocal cords, which may result in increased absorption of HA. Decreased blood flow and reduced inflammation have been associated with a longer duration of action.[52] As IMT may contribute to this, it might be an ideal training after HA injection laryngoplasty.

TABLE 3.
Influence of IMT Intervention on Odds of Improvement in NGGA, BI, VHI-10 and VOS Scores

	Changes in Scores			Percentages of Score Changes		
	OR*	95%CI	*P* Value	OR*	95%CI	*P* Value
NGGA						
IMT	2.34	(0.47, 13.27)	0.3401	13.05	(2.03, 156.39)	0.0212
Duration of vocal disease	0.89	(0.46, 1.03)	0.2938	0.92	(0.75, 1.03)	0.2947
BMI	0.99	(0.82, 1.18)	0.8835	0.99	(0.82, 1.2)	0.9288
GERD	1.41	(0.28, 7.88)	0.6996	3.91	(0.62, 44.41)	0.2084
BI						
IMT	2.14	(0.43, 12.48)	0.3963	3.29	(0.62, 22.1)	0.2038
Duration of vocal disease	0.91	(0.57, 1.03)	0.3072	0.89	(0.55, 1.01)	0.1931
BMI	1.08	(0.91, 1.3)	0.4425	1.16	(0.97, 1.46)	0.1509
GERD	1.66	(0.33, 9.35)	0.5691	1.45	(0.27, 8.54)	0.6833
VHI-10						
IMT	3.25	(0.59, 24.4)	0.2271	2.94	(0.52, 23.15)	0.2745
Duration of vocal disease	0.91	(0.54, 1.03)	0.3059	0.92	(0.56, 1.03)	0.3106
BMI	1.09	(0.91, 1.34)	0.3928	1.15	(0.96, 1.45)	0.1842
GERD	6.25	(1.08, 49.34)	0.0674	6.24	(1.07, 50.03)	0.0693
VOS						
IMT	0.86	(0.16, 4.83)	0.8695	2.64	(0.51, 18.06)	0.3010
Duration of vocal disease	0.97	(0.79, 1.09)	0.7212	0.97	(0.84, 1.08)	0.6350
BMI	1.09	(0.91, 1.32)	0.4109	1.09	(0.92, 1.31)	0.3836
GERD	2.01	(0.4, 10.96)	0.4315	2.22	(0.42, 14.65)	0.3933

* When the independent variable was categorical (i.e., IMT or GERD), the OR value indicated the odds ratio of experiencing higher score improvement in the presence vs.absence of the independent variable. When the independent variable was continuous, the OR value indicated the odds ratio of experiencing higher score improvement for every unit increase of the independent variable (i.e., for every one month increase in diagnosis duration of vocal disease, or for every unit increase in BMI).Abbreviations: BI, Bowing index; BMI, body mass index; GERD, gastroesophageal reflux disease; IMT, inspiratory muscle training; NGGA, normalized glottal gap area; OR, odds ratio; VHI-10, voice handicap index-10; VOS, voice outcome survey.

In addition to the glottal gap, vocal bowing is another common characteristic in patients with vocal insufficiency.[4] Various mechanisms for vocal fold bowing have been hypothesized, including intubation-related damage to the laryngeal mucosa, vocal fold stiffening, vocal fold paresis, sulcus vocalis, or laryngeal atrophy; but its actual cause is unknown[53] The treatment of bowed vocal folds has focused on therapeutic injections or thyroplasty (medialization laryngoplasty).[15] In our study, no significant difference was found in the BI between the two groups. A previous study found that in patients who underwent vocal function exercises, BI was not able to reflect changes or improvements in various voice measures, even though the self-assessment of voice had improved.[54] A previous study also revealed that IMT did not result in a change in BI.[55] In these studies, vocal function improved, even in the absence of a change in bowing. As IMT enhances the coordination between the respiratory and laryngeal systems, the effect of vocal bowing may be neutralized. NGGA and BI are both scaled to present glottic closure. In our study, IMT reduced the glottal gap in terms of NGGA, whereas BI revealed no significant changes. This might imply that BI is relatively insensitive to changes in the glottic gap when compared to NGGA.[56]

Furthermore, we found that VHI-10 and VOS scores improved in both groups, but with no significant differences between groups. This supports the benefit of HA injection in enhancing patients' voice quality[57,58]; however, it implies that the implementation of IMT may not provide additional benefits in voice quality, or the changes in voice outcomes were too small to be perceived by patients' subjective feelings. The limited effect of IMT on voice outcome in our study might be explained by two aspects. First, VHI-10 and VOS scores were patient-reported, and there might be a wide variation in the subjective perception of voice performance from different individuals in terms of similar voice performance. Both emotional and physical effects may affect the outcome, thus compared to other assessing tools, VHI has not been consistently always found to be correlated well with clinicians' assessments of clinicians.[59] In future studies involving voice outcome evaluation, it might be more appropriate to apply more objective assessing tools, such as the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) and the grade, roughness, breathiness, asthenia, and strain (GRBAS) scale, which are assessed by professionals, to reduce inter-rater difference. Second, it is possible that the effect of injection laryngoplasty in patients' voice improvement was so obvious,[58] that the effect of IMT turned out to be too modest and ambiguous to be perceived by patients' subjective feelings. Even if earlier studies suggested that IMT might be able to improve VHI within 4 weeks,[45,60] the patient populations were different from that in our study. All the patients included in this study had undergone injection laryngoplasty, and therefore the effect of the 3-month IMT training may have been relatively small when compared to the effect of the injection.

To our knowledge, this is the first study to evaluate the effects of additional IMT after HA injection on glottic closure and the voice outcome in patients with glottic insufficiency. The results supported that IMT could improve glottal closure by up to 27% and can serve as pilot evidence to encourage future evaluations.

Our study has some limitations. First, it was difficult to assess the adherence to training of the patients. In our protocol, IMT was a 3 month-long program that required patients to exercise by themselves at home; therefore, compliance was difficult to monitor. In addition, the IMT intensity was not evaluated in our study, and the sample size was small, which would hamper statistical power. Finally, we evaluated only the effects of IMT in this study. Further studies are needed to explore different types of respiratory muscle training protocols in patients with vocal cord diseases to provide more evidence.

CONCLUSION

Inspiratory muscle training improved glottal closure in patients with vocal cord insufficiency who were treated with HA injection laryngoplasty. In addition to traditional voice therapy, IMT may be an easy, self-administered management technique after injection laryngoplasty. Future studies with larger population sizes can provide more information on the effects of IMT or RMT at different durations and intensities.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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REFERENCES

1. Stachler RJ, Francis DO, Schwartz SR, et al. Clinical practice guideline: hoarseness (Dysphonia) (Update). *Otolaryngol Head Neck Surg.*. 2018;158(1_suppl):S1–s42. https://doi.org/10.1177/0194599817751030.
2. McGarey Jr. PO, Bitar R, Hughes CK, et al. Correlation of glottic gap and voice impairment in presbyphonia. *Laryngoscope*. 2021;131:1594–1598. https://doi.org/10.1002/lary.29068.
3. Zhang Z. Mechanics of human voice production and control. *J Acoust Soc Am*. 2016;140:2614. https://doi.org/10.1121/1.4964509.
4. Onwordi LN, Al Yaghchi C. *Airway Glottic Insufficiency*. StatPearls Publishing LLC; 2022.
5. Jiang J, Lin E, Hanson DG. Vocal fold physiology. *Otolaryngol Clin North Am*. 2000;33:699–718. https://doi.org/10.1016/s0030-6665(05)70238-3.
6. Giraldez-Rodriguez LA, Johns M. Glottal insufficiency with aspiration risk in dysphagia. *Otolaryngol Clin North Am*. 2013;46:1113–1121. https://doi.org/10.1016/j.otc.2013.09.004.
7. Rosenthal LH, Benninger MS, Deeb RH. Vocal fold immobility: a longitudinal analysis of etiology over 20 years. *Laryngoscope*. 2007;117:1864–1870. https://doi.org/10.1097/MLG.0b013e3180de4d49.
8. Belafsky PC, Postma GN, Reulbach TR, et al. Muscle tension dysphonia as a sign of underlying glottal insufficiency. *Otolaryngol Head Neck Surg*. 2002;127:448–451. https://doi.org/10.1067/mhn.2002.128894.
9. Wang CT, Liao LJ, Huang TW, et al. Preliminary report of vocal fold augmentation with cross-linked porcine collagen. *Otolaryngol Head Neck Surg*. 2012;146:606–610. https://doi.org/10.1177/0194599811434003.
10. Ford CN, Bless DM. Clinical experience with injectable collagen for vocal fold augmentation. *Laryngoscope*. 1986;96:863–869. https://doi.org/10.1002/lary.1986.96.8.863.
11. Accordi M, Ferrero FE, Galceràn M, et al. Treatment of glottic insufficiency with intracordal implant of hydron gel: phoniatric evaluation. *Acta Otorhinolaryngol Ital*. 1987;7:87–100.
12. Hsiung MW, Lin YS, Su WF, et al. Autogenous fat injection for vocal fold atrophy. *Eur Arch Otorhinolaryngol*. 2003;260:469–474. https://doi.org/10.1007/s00405-003-0622-y.
13. Gutowski KA. Hyaluronic acid fillers: science and clinical uses. *Clin Plast Surg*. 2016;43:489–496. https://doi.org/10.1016/j.cps.2016.03.016.
14. Bertroche JT, Radder M, Kallogjeri D, et al. Patient-defined duration of benefit from juvederm (hyaluronic acid) used in injection laryngoplasty. *Laryngoscope*. 2019;129:2744–2747. https://doi.org/10.1002/lary.27842.
15. Mallur PS, Rosen CA. Vocal fold injection: review of indications, techniques, and materials for augmentation. *Clin Exp Otorhinolaryngol*. 2010;3:177–182. https://doi.org/10.3342/ceo.2010.3.4.177.
16. Jang JY, Lee G, Ahn J, et al. Early voice rehabilitation with injection laryngoplasty in patients with unilateral vocal cord palsy after thyroidectomy. *Eur Arch Otorhinolaryngol*. 2015;272:3745–3750. https://doi.org/10.1007/s00405-015-3720-8.
17. Jeong GE, Lee DH, Lee YS, et al. Treatment efficacy of voice therapy following injection laryngoplasty for unilateral vocal fold paralysis. *J Voice*. 2022;36:242–248. https://doi.org/10.1016/j.jvoice.2020.05.014.
18. Belsky MA, Shelly S, Rothenberger SD, et al. Phonation resistance training exercises (PhoRTE) with and without expiratory muscle strength training (EMST) for patients with presbyphonia: a noninferiority randomized clinical trial. *J Voice*. 2021:S0892−1997(21)00077−1. https://doi.org/10.1016/j.jvoice.2021.02.015.
19. Lowell SY, Colton RH, Kelley RT, et al. Isolated and combined respiratory training for muscle tension Dysphonia: preliminary findings. *J Voice*. 2022;36:361–382. https://doi.org/10.1016/j.jvoice.2020.06.013.
20. Sapienza CM, Wheeler K. Respiratory muscle strength training: functional outcomes vs.plasticity. *Semin Speech Lang*. 2006;27:236–244. https://doi.org/10.1055/s-2006-955114.
21. Desjardins M, Bonilha HS. The impact of respiratory exercises on voice outcomes: a systematic review of the literature. *J Voice*. 2020;34:648.e1–648.e39. https://doi.org/10.1016/j.jvoice.2019.01.011.
22. Göhl O, Walker DJ, Walterspacher S, et al. Respiratory muscle training: state of the art. *Pneumologie*. 2016;70:37–48. https://doi.org/10.1055/s-0041-109312.
23. Liaw MY, Hsu CH, Leong CP, et al. Respiratory muscle training in stroke patients with respiratory muscle weakness, dysphagia, and dysarthria - a prospective randomized trial. *Medicine (Baltimore)*. 2020;99:e19337. https://doi.org/10.1097/md.0000000000019337.
24. Mackała K, Kurzaj M, Okrzymowska P, et al. The effect of respiratory muscle training on the pulmonary function, lung ventilation, and endurance performance of young soccer players. *Int J Environ Res Public Health*. 2019;17:234. https://doi.org/10.3390/ijerph17010234.
25. Menezes KK, Nascimento LR, Ada L, et al. Respiratory muscle training increases respiratory muscle strength and reduces respiratory complications after stroke: a systematic review. *J Physiother*. 2016;62:138–144. https://doi.org/10.1016/j.jphys.2016.05.014.

26. Ferreira GD, Costa AC, Plentz RD, et al. Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis. *Physiotherapy*. 2016;102:221–228. https://doi.org/10.1016/j.physio.2016.01.002.
27. Montero Ferro A, R PB-V, Moreira Mello RL, et al. Effects of inspiratory muscle training on respiratory muscle strength, lung function, functional capacity and cardiac autonomic function in Parkinson's disease: randomized controlled clinical trial protocol. *Physiother Res Int*. 2019;24:e1777. https://doi.org/10.1002/pri.1777.
28. Wang Q, Yang F, Gao L, et al. Effects of inspiratory muscle training and high-intensity interval training on lung function and respiratory muscle function in Asthma. *Respir Care*. 2022. https://doi.org/10.4187/respcare.09813.
29. Tsai YC, Huang S, Che WC, et al. The effects of expiratory muscle strength training on voice and associated factors in medical professionals with voice disorders. *J Voice*. 2016;30:759.e21–759.e27. https://doi.org/10.1016/j.jvoice.2015.09.012.
30. Reyes A, Castillo A, Castillo J, et al. The effects of respiratory muscle training on phonatory measures in individuals with parkinson's disease. *J Voice*. 2020;34:894–902. https://doi.org/10.1016/j.jvoice.2019.05.001.
31. Omori K, Kacker A, Slavit DH, et al. Quantitative videostroboscopic measurement of glottal gap and vocal function: an analysis of thyroplasty type I. *Ann Otol Rhinol Laryngol*. 1996;105:280–285. https://doi.org/10.1177/000348949610500407.
32. Omori K, Slavit DH, Matos C, et al. Vocal fold atrophy: quantitative glottic measurement and vocal function. *Ann Otol Rhinol Laryngol*. 1997;106(7 Pt 1):544–551. https://doi.org/10.1177/000348949710600702.
33. Rueden CT, Schindelin J, Hiner MC, et al. ImageJ2: ImageJ for the next generation of scientific image data. *BMC Bioinformatics*. 2017;18:529. https://doi.org/10.1186/s12859-017-1934-z.
34. Rosen CA, Lee AS, Osborne J, et al. Development and validation of the voice handicap index-10. *Laryngoscope*. 2004;114:1549–1556. https://doi.org/10.1097/00005537-200409000-00009.
35. Gliklich RE, Glovsky RM, Montgomery WW. Validation of a voice outcome survey for unilateral vocal cord paralysis. *Otolaryngol Head Neck Surg.*. 1999;120:153–158. https://doi.org/10.1016/s0194-5998(99)70399-2.
36. Fang TJ, Li HY, Gliklich RE, et al. Assessment of Chinese-version voice outcome survey in patients with unilateral vocal cord paralysis. *Otolaryngol Head Neck Surg.*. 2007;136:752–756. https://doi.org/10.1016/j.otohns.2006.11.048.
37. Lam PK, Chan KM, Ho WK, et al. Cross-cultural adaptation and validation of the Chinese Voice Handicap Index-10. *Laryngoscope*. 2006;116:1192–1198. https://doi.org/10.1097/01.mlg.0000224539.41003.93.
38. Titze IR, Lemke J, Montequin D. Populations in the U.S. workforce who rely on voice as a primary tool of trade: a preliminary report. *J Voice*. 1997;11:254–259. https://doi.org/10.1016/s0892-1997(97)80002-1.
39. Ayoub MR, Larrouy-Maestri P, Morsomme D. The effect of smoking on the fundamental frequency of the speaking voice. *J Voice*. 2019;33:802.e11–802.e16. https://doi.org/10.1016/j.jvoice.2018.04.001.
40. Byeon H. The risk factors related to voice disorder in teachers: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2019;16:3675. https://doi.org/10.3390/ijerph16193675.
41. Reiter R, Hoffmann TK, Pickhard A, et al. Hoarseness-causes and treatments. *Dtsch Arztebl Int*. 2015;112:329–337. https://doi.org/10.3238/arztebl.2015.0329.
42. Ruddy BH, Davenport P, Baylor J, et al. Inspiratory muscle strength training with behavioral therapy in a case of a rower with presumed exercise-induced paradoxical vocal-fold dysfunction. *Int J Pediatr Otorhinolaryngol*. 2004;68:1327–1332. https://doi.org/10.1016/j.ijporl.2004.04.002.
43. Mathers-Schmidt BA, Brilla LR. Inspiratory muscle training in exercise-induced paradoxical vocal fold motion. *J Voice*. 2005;19:635–644. https://doi.org/10.1016/j.jvoice.2005.03.005.
44. Sapienza CM, Brown J, Martin D, et al. Inspiratory pressure threshold training for glottal airway limitation in laryngeal papilloma. *J Voice*. 1999;13:382–388. https://doi.org/10.1016/s0892-1997(99)80043-5.
45. Baker SE, Sapienza CM, Martin D, et al. Inspiratory pressure threshold training for upper airway limitation: a case of bilateral abductor vocal fold paralysis. *J Voice*. 2003;17:384–394. https://doi.org/10.1067/s0892-1997(03)00066-3.
46. Zeren M, Demir R, Yigit Z, et al. Effects of inspiratory muscle training on pulmonary function, respiratory muscle strength and functional capacity in patients with atrial fibrillation: a randomized controlled trial. *Clin Rehabil*. 2016;30:1165–1174. https://doi.org/10.1177/0269215515628038.
47. Sandnes A, Andersen T, Clemm HH, et al. Clinical responses following inspiratory muscle training in exercise-induced laryngeal obstruction. *Eur Arch Otorhinolaryngol*. 2022;279:2511–2522. https://doi.org/10.1007/s00405-021-07214-5.
48. Castillo A, Castillo J, Reyes A. Association between subglottic pressure and pulmonary function in individuals with Parkinson's disease. *J Voice.*. 2020;34:732–737. https://doi.org/10.1016/j.jvoice.2019.03.001.
49. Kobayashi I, Kondo T, Suzuki H, et al. Expiratory activity of the inspiratory muscles during cough. *Jpn J Physiol*. 1992;42:905–916. https://doi.org/10.2170/jjphysiol.42.905.
50. Zhang Z. The physical aspects of vocal health. *Acoust Today*. 2021;17:60–68. https://doi.org/10.1121/at.2021.17.3.60.
51. Zhang Z. Regulation of glottal closure and airflow in a three-dimensional phonation model: implications for vocal intensity control. *J Acoust Soc Am*. 2015;137:898–910. https://doi.org/10.1121/1.4906272.
52. Chang J, Courey MS, Al-Jurf SA, et al. Injection laryngoplasty outcomes in irradiated and nonirradiated unilateral vocal fold paralysis. *Laryngoscope*. 2014;124:1895–1899. https://doi.org/10.1002/lary.24622.
53. Lagorio LA, Carnaby-Mann GD, Crary MA. Treatment of vocal fold bowing using neuromuscular electrical stimulation. *Arch Otolaryngol Head Neck Surg*. 2010;136:398–403. https://doi.org/10.1001/archoto.2010.33.
54. Kaneko M, Hirano S, Tateya I, et al. Multidimensional analysis on the effect of vocal function exercises on aged vocal fold atrophy. *J Voice*. 2015;29:638–644. https://doi.org/10.1016/j.jvoice.2014.10.017.
55. Desjardins M, Halstead L, Simpson A, et al. Respiratory muscle strength training to improve vocal function in patients with presbyphonia. *J Voice*. 2022;36:344–360. https://doi.org/10.1016/j.jvoice.2020.06.006.
56. Stager SV, Gupta S, Amdur R, et al. Objective laryngoscopic measures from older patients with voice complaints and signs of aging. *J Speech Lang Hear Res*. 2021;64:4705–4717. https://doi.org/10.1044/2021_jslhr-21-00095.
57. Oguz H, Demirci M, Arslan N, et al. Long-term voice results of injection with hyaluronic acid-dextranomere in unilateral vocal fold paralysis. *Acta Otolaryngol*. 2013;133:513–517. https://doi.org/10.3109/00016489.2012.750034.
58. Wang CC, Wu SH, Tu YK, et al. Hyaluronic acid injection laryngoplasty for unilateral vocal fold paralysis-A systematic review and meta-analysis. *Cells*. 2020;9:2417. https://doi.org/10.3390/cells9112417.
59. Childs LF, Bielinski C, Toles L, et al. Relationship between patient-perceived vocal handicap and clinician-rated level of vocal dysfunction. *Laryngoscope*. 2015;125:180–185. https://doi.org/10.1002/lary.24889.
60. Desjardins M, Halstead L, Simpson A, et al. Respiratory muscle strength training to improve vocal function in patients with presbyphonia. *J Voice*. 2020;36:344–360. https://doi.org/10.1016/j.jvoice.2020.06.006.