Title: Respiratory Muscle Strength Training to Improve the Vocal Function of Patients with Presbyphonia

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PROTOCOL TITLE:

Respiratory Muscle Strength Training to Improve the Vocal Function of Patients with Presbyphonia

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1.0 Objectives / Specific Aims

More than 10 million Americans over 65 years of age have presbyphonia, which is characterized by age-related vocal fold atrophy that impairs their ability to speak at a normal volume for a normal amount of time. Surgery can be used to treat presbyphonia, but non-invasive methods (voice exercises) are preferred given the general risks of surgery and anesthesia in older individuals. Vocal Function Exercises (VFE), the predominate type of voice exercises used to treat presbyphonia, can improve voice quality, but the outcomes remain suboptimal, with many patients unable to successfully communicate, leading to frustration, social isolation and feelings of helplessness.

Importantly, voice exercises target vocal fold strengthening, but underutilizes a potentially crucial second pathway for intervention: strengthening the respiratory system. In addition to vocal fold integrity, adequate vital capacity (airflow) and subglottal pressure are crucial for voice production. Many clinicians do indeed devote time in their therapy sessions to 'breathing exercises' (diaphragmatic breathing) but these are not evidence-based, and they are unlikely to adequately strengthen respiratory muscles to impact the critical components of pulmonary function that effect voice. Therefore, a targeted approach to improve the function of the respiratory system through rigorous and clinically feasible respiratory training (training of the respiratory muscles) could augment VFE and improve voice efficiency and quality in patients with presbyphonia.

The potential of respiratory training to improve respiratory and voice outcomes in patients with presbyphonia is particularly relevant when one considers that the older population usually has coexisting age-related declines in respiratory function. The clinical impact of respiratory training could be high, since it is a low-cost/low-risk approach that can be used in clinic and at home, be delivered during voice therapy sessions, and have a synergistic effect with voice exercises.

There are two main types of respiratory training: inspiratory training, also called inspiratory muscle strength training (IMST), and expiratory training, also called expiratory muscle strength training (EMST) . In this application, we propose a novel, proof-of-concept study to test whether the addition of either type of respiratory training to the standard of care voice therapy (voice exercises) enhances respiratory and voice outcomes. This study will permit, for the first time, the comparison between inspiratory and expiratory training. The theoretical framework is: inspiratory training strengthens the inspiratory muscles and thus increases both vital capacity and the ability to counteract passive recoil of the lungs, improving

the quantity of and control over the airflow available to drive the vocal folds. Expiratory training strengthens the expiratory muscles to expand the expiratory reserve volume and provide more airflow for voicing. Using pulmonary function tests and respiratory pressure measures, combined with voice assessments, we will specifically evaluate our hypotheses and determine the independent effects of inspiratory training and expiratory training on respiratory function and voice production. We will also evaluate the interaction between the type of respiratory training and a patient's baseline respiratory function. This will provide mechanistic information to guide the future selection of the type of respiratory training to augment voice therapy, to promote an impairment-specific intervention paradigm.

Forty-eight participants diagnosed with presbyphonia will be included in the study and will be stratified and blocked-randomized into one of the three intervention groups (two experimental groups and one control group), using a 3-parallel arm design: 1) inspiratory training (IMST) (experimental group), 2) expiratory training (EMST) (experimental group), or 3) voice exercises (VFE) (control group), delivered four times during a 60-minute therapy session. Monitored home practice will consist of 10 minutes of twice daily exercise for the duration of therapy. Participants from all three groups will carry on with their standard of care voice therapy with a certified SLP.

Specific Aim 1: To measure the effects of respiratory training on respiratory and voice outcomes in patients with presbyphonia. Hypothesis 1: The respiratory training groups (inspiratory and/or expiratory) will demonstrate greater improvement in respiratory outcomes, measured through pulmonary function tests and respiratory pressure measures, compared with the voice exercises-only group. Hypothesis 2: The respiratory training groups (inspiratory and/or expiratory) will demonstrate greater improvement in voice-related outcomes than the voice exercises-only group.

Secondary Aim 1: To assess the reliability of the ratings for subjective outcomes (videostroboscopy ratings and perceptual judgements of voice quality). Hypothesis 1: Intra-judge reliability will be of at least 80%. Hypothesis 2: Inter-judge reliability will be of at least 70%.

Specific Aim 2: To determine how baseline measures of respiratory function influence the effects of respiratory training (respiratory and voice outcomes). Hypothesis 1: inspiratory training will have maximal effect on patients with decreased maximum inspiratory pressure (MIP). Hypothesis 2: Expiratory will have maximal effect on patients with decreased maximum expiratory pressure (MEP).

This is an initial feasibility and mechanistic study that has the potential to reveal that respiratory training can significantly improve outcomes from voice therapy by acting in synergy with voice exercises. Currently,

much time is spent in voice therapy on subthreshold 'breathing exercises' that lack evidence. This project will provide guidance for evidence-based and theory driven approaches to leverage respiratory function to improve voice therapy. Conversely, negative findings from this study would indicate that respiratory function is ineffective and not a viable target for therapy in this patient population.

2.0 Background

Presbyphonia is characterized by vocal fold atrophy and a gap between the vocal folds. It impacts more than 10 million Americans, inhibiting their ability to speak at a normal volume for a usual duration(1). Disability related to presbyphonia is increasing due to: 1) the large number of older adults who work and 2) the expanding population over 65(2). Currently, non-invasive rehabilitation targeting laryngeal function is the main treatment for presbyphonia, since surgery is associated with increased risk of negative outcomes in older individuals and often results in suboptimal voice quality(3-5). While voice exercises improve voice quality in patients with presbyphonia, many patients are unable to successfully communicate in their environment even after completing treatment, i.e., they are unable to be heard unless close to their conversational partner, cannot be heard in the setting of background noise, or are unable to produce normal utterance lengths without taking frequent pauses to breathe. Presbyphonia is a well-known cause of reduced quality of life and social isolation(1, 6-8).

Current therapeutic approaches underutilize a second pathway for intervention – strengthening the respiratory system. Adequate vital capacity (airflow) and subglottal pressure are necessary to drive voice production. While many clinicians devote substantial time in their therapy sessions to breathing exercises, specifically diaphragmatic breathing, these exercises are not evidence-based and are unlikely to adequately lead to neuromuscular and pulmonary function changes. Improving the respiratory support for speech through rigorous respiratory training would, in theory, augment voice exercises to increase vocal efficiency in patients with presbyphonia. The coexisting age-related declines in respiratory function (in lung elasticity, ribcage mobility and inspiratory and expiratory muscle strength) further support respiratory training's potential to improve respiratory and voice outcomes in patients with presbyphonia(9-12). Additionally, respiratory training is a low-cost/low-risk approach that patients can use in clinic and at home to improve clinical measures of respiratory muscle strength and pulmonary function(13, 14).

There are two types of respiratory training: inspiratory and expiratory. Inspiratory and expiratory training have different physiological targets and result in unique and specific changes to respiratory function(13). Inspiratory training increases vital capacity, specifically inspiratory volume, and inspiratory muscle strength, to counteract passive recoil from positive pressures(15-17). The improved respiratory function from inspiratory training would increase the amount of air to drive the vocal folds and allow for better control of airflow with the respiratory system (to compensate for the lack of vocal fold closure). Expiratory training increases vital capacity, specifically expiratory reserve volume, and expiratory muscle strength to allow for increased contraction of the rib cage and abdominal muscles, thus providing access to more air to drive the vocal folds(18, 19). The effects of increasing respiratory muscle strength, either inspiratory or expiratory, have never been studied in patients with presbyphonia. Such an investigation, as we are proposing, would improve our mechanistic understanding of the cross-system interaction for voicing between laryngeal and respiratory function, and indicate the potential for inspiratory or expiratory respiratory training as viable therapy modalities for patients with presbyphonia.

The objective of respiratory training is to strengthen the respiratory muscles using a hand-held pressure threshold device in which patients breathe in (inspiratory training) or out (expiratory training) forcefully to open a valve and allow air to flow. The overloading of the respiratory muscles activates the neuromuscular system beyond its normal level of activity and forces the system to adapt, which results in changes in muscle function(20). Previous studies confirm that respiratory training induces morphologic changes in the respiratory muscles. In a study by Ramirez-Sarmiento et al.(21), post-intervention biopsies were taken from the external intercostal muscles and the results revealed a 38% increase in the proportion of type I fibers and a 21% increase in the size of type II fibers (21). Inspiratory and expiratory training have also been found to improve maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), respectively, as well as spirometry outcomes in different populations, including elderly individuals (15, 22). In the voice literature, inspiratory training studies have targeted increasing MIP to reduce dyspnea in patients with upper airway obstruction diseases such as paradoxical vocal fold movement disorder, recurrent laryngeal papilloma and bilateral abductor vocal fold paralysis (23-25). We were unable to find published research on voice quality outcomes from inspiratory training. As for expiratory training, three studies have assessed its effect on professional voice users with voice complaints (26-28). Improved subglottal pressure at loud intensity and reductions in vocal symptoms were found when combining voice therapy and expiratory training in patients with laryngeal irritation, edema, and/or benign vocal fold lesions(28).

The effects of respiratory training on voice outcomes have never been studied on patients with presbyphonia despite the declines in respiratory function that occur with aging. Both inspiratory and expiratory pressures can be reduced in elderly patients, yielding different impairment profiles(10). Since inspiratory muscles are crucial for increasing inspiratory lung volume and for counteracting expiratory pressures to enhance airflow control during sustained speech, increasing their strength appears to be a viable target to improve the loudness and duration of speech(29). However, some individuals may have difficulty generating sufficient subglottal pressure despite initiating phonation at high lung volume because of reduced ribcage compliance and lung recoil forces(11, 12). For those patients, early activation of the expiratory muscles might be the most effective strategy to increase vocal efficiency, by compressing the chest wall to a smaller volume and generating the required airway pressure for speech production (19, 30). These patients may optimally benefit from expiratory training. Although some patients may benefit from both inspiratory and expiratory training, there is a need to assess the individual effects of both interventions prior to testing their combined effect in a future study to understand the mechanism of action and optimize the use of therapy time. Thus, we propose to study how differences in patients' baseline respiratory function impacts intervention response, specifically which patients benefit from inspiratory training and which patients benefit from expiratory training.

The contributions of this study will be to: 1) assess the relevance of respiratory training when treating patients with presbyphonia; 2) determine the mechanistic respiratory and voice effects of respiratory training for patients with presbyphonia, and 3) identify profiles of patients likely to benefit from each type of respiratory training. These contributions would be significant as they would begin to provide speech language pathologists (SLPs) with evidence pertaining to rigorous respiratory training for presbyphonic patients. After the study results are validated, SLPs will be able to determine, based on their clinical assessment, which patients should undergo respiratory training and which modality would be maximally beneficial, inspiratory or expiratory training, or both. This would improve the outcomes and efficiency of voice therapy. If respiratory training results in meaningful voice quality changes for patients with presbyphonia, it may also indicate a novel modality for use with other hypofunctional voice disorders (e.g. adductor paralysis).

3.0 Intervention to be studied

Participants in all groups will have already undertaken their voice care (voice assessments and voice therapy with a certified SLP) at MUSC. Depending on their group assignment, participants will also receive either inspiratory training, expiratory training, or no respiratory intervention (standard of care group). The experimental and standard of care interventions are described below.

Inspiratory Training [Experimental intervention]: Inspiratory training will be conducted using an inspiratory pressure threshold trainer (Philips Respironics® Threshold IMT or POWERbreathe® Medic Plus, for patients with a MIP of 55 cmH_20 and over), which consists of a mouthpiece with a spring-loaded valve(13, 25). The valve blocks the airflow until the threshold pressure is achieved and allows airflow as long as the sufficient pressure is maintained. The threshold will be set at 75% of the participant's initial MIP, as reported in the literature with elderly participants(16). If it is too hard for the participant, the load will be lowered until the participant is able to perform the exercises. The load will be adjusted weekly by the study team member to maintain a threshold at 75% of the participant's MIP. Daily practices will consist of 5 sets of 5 breaths with the device with a break between sets, repeated twice daily (15, 18, 31).

Expiratory Training [Experimental intervention]: Expiratory training will be conducted using an expiratory pressure threshold trainer (EMST150™) which consists of a mouthpiece with a spring-loaded valve. The valve blocks the airflow until the threshold pressure is produced (set at 75% of the participant's initial MEP, per literature with similar age groups(32-34)), and allows the airflow as long as the sufficient pressure is maintained. Participants will be asked to exhale forcefully into the mouthpiece after a full inspiration. If it is too hard for the participant, the load will be lowered until the participant is able to perform the exercises. The load will be adjusted weekly by the study team member to maintain a threshold at 75% of the participant's MEP. Daily practices will consist of 5 sets of 5 breaths with the device with a break between sets, repeated twice daily(32-34).

Inspiratory and expiratory training have never been conducted on patients with presbyphonia. To determine the adequate intensity and duration of treatment, we reviewed the literature of respiratory training interventions with patients of similar age groups. We decided on a threshold of 75% of MIP and MEP because 1) this value was widely used across studies, resulted in significant improvements in respiratory outcomes, and has been shown to be safe(16, 32-34); 2) maximal improvements in muscle strength have been reported to occur with a loading at 70-90% of the maximal strength(14). The regimen of 5 sets of 5 breaths was also widely used across studies, along with a threshold at 75% of MIP/MEP, and resulted in improved respiratory outcomes. We chose to have the participants practice their exercises every

day of the week because in our opinion it is the best way to create a habit and therefore enhance compliance to treatment.

Voice Exercises [Standard of care intervention]: Participants will be instructed to follow the four steps of the VFE protocol, developed by Stemple (35) and commonly used by SLPs with patients with presbyphonia: (a) sustain the vowel /i/ on the musical note F (above middle C for women; below middle C for men) for as long as possible. (b) Glide from the lowest note to the highest note on the word "knoll". (c) Glide from the highest note to the lowest note of the word "knoll". (d) Sustain the notes C-D-E-F-G (starting from middle C for women and an octave below middle C for men) on the word "oll", for as long as possible. Each note will be repeated until the participant finds the right placement (forward-focused voice), as judged by the SLP. Humming exercises will be used to facilitate placement. Daily practices, 2x/day, will consist of two repetitions of the VFE protocol for the IMST and EMST groups and four repetitions of the VFE protocol for the VFE group. Recordings of the therapy sessions will be provided to facilitate home practice.

4.0 Study Endpoints

The outcome measures have been chosen to provide the most complete and accurate evaluation of therapy results. Outcome measures are numerous in the voice field, and to allow comparison across studies, the American Speech-Language-Hearing Association (ASHA) has recently developed a recommended protocol for instrumental assessment of voice(36). We modeled our measurement methods on these recommendations and added supplementary outcomes relevant to this study.

Voice measures. [Note: voice measurements will be obtained from the participants' standard of care voice assessments]

Videostroboscopy: Recordings of vocal fold vibration from sustained phonations of /i/ at various pitch and loudness levels will be used 1) to assess the parameters described in the Voice-Vibratory Assessment with Laryngeal Imaging (VALI) rating form(37), and 2) for measurements of normalized glottal gap (NGG)(38).

Acoustic measures: The Computerized Speech Lab (CSL) is used to record sustained phonation at various pitch and intensity levels, reading of the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V)(40) sentences, as well as a short natural conversation with the SLP. Acoustic analysis will include: 1) measures of voice intensity: habitual and maximum sound pressure levels (SPL); 2) measures of fundamental

frequency (F0): mean, minimum, and maximum vocal F0, and 3) measures of voice quality: cepstral peak, jitter, shimmer, and harmonics-to-noise ratio.

Perceptual judgments of voice quality: The CAPE-V(40) rating form will be used for the judgment of voice quality of sustained phonation, reading and conversational speech tasks recorded via CSL. The CAPE-V form includes ratings of overall severity, roughness, breathiness, strain, pitch, and loudness, as well as qualitative information about resonance and additional features.

Patient self-assessments: Patients are asked to complete the 1) Voice Handicap Index (VHI): a questionnaire that evaluates the degree of handicap experienced by the patient in relation to their voice use(41); 2) the GFI(42): a validated disease-specific impairment instrument conceived to assess symptoms related to glottal insufficiency; 3) the RSI(43), a validated self-administered questionnaire to assess symptoms related to LPR; and 4) the Communicative Participation Item Bank (CPIB) general short form(44). Patients are also asked to rate their perceived phonatory effort (PPE) on a direct magnitude estimation scale(45) following the speaking and voicing tasks recorded with the CSL.

Aerodynamic measures: The Phonatory Aerodynamic System (PAS) is used to measure 1) mean glottal airflow rate: estimated from sustained phonation of a vowel(36); 2) average subglottal air pressure (P_s): measured during the production of a voiceless plosive consonant (/p/) at normal pitch and loudness, an accepted indirect and non-invasive measurement method for P_s (46); and 3) laryngeal resistance: calculated by dividing subglottal pressure by mean glottal airflow.

Phonation duration (MPT): The maximum phonation duration of the vowel /a/ is measured via CSL.

<u>Respiratory measures (respiratory measures will be recorded solely as part of the study)</u>.

Spirometry: Spirometry will be used to measure 1) forced vital capacity (FVC), 2) forced expiratory volume in one second (FEV1), and calculate the 3) FEV1/FVC ratio. The predicted values (%) of these three measures will also be reported. The patient will be asked to take a full inspiration, blow out the air forcefully and then exhale slowly to residual volume in the spirometer. The task is repeated at least three times, until the two best measurements differ by no more than 0.15.

Muscle pressure measures: 1) MIP: measured at functional residual capacity, is an indicator of inspiratory muscle strength. Patients will be instructed to exhale fully and then inhale with maximal effort with lips sealed to the pressure meter for at least 2 seconds. 2) MEP: measured at full lung capacity, is an indicator of expiratory muscle strength. Participants will be instructed to take a full breath and then exhale with maximal force with lips sealed to the pressure meter for at least 2 seconds.

5.0 Inclusion and Exclusion Criteria/ Study Population

Patients who are diagnosed with presbyphonia and who have already sought and begun voice care at MUSC, will undergo a brief screening interview by Dr. Halstead, after which qualifying patients will be offered participation in the study. A study team member will meet with interested participants and will provide a thorough description of the study prior to obtaining formal written consent. Participants who don't meet stratification requirements will be excluded from the study.

Inclusion Criteria

The participant:

- must receive a diagnosis of presbyphonia by a trained laryngologist. The diagnosis will be given following a visual examination of the larynx if the observations are consistent with the characteristics of a presbylarynx, as judged by the laryngologist.
- must have already undertaken their voice care at MUSC
- must be 50 years and older
- must be English-speaking
- must sign the informed consent

Exclusion Criteria

The participant

- has received voice therapy in the past year (other than current care)
- presents with a vocal fold pathology other than presbyphonia
- has a known neurologic or a progressive neuromuscular disease
- doesn't meet the stratification requirements for muscle pressure
- has a medical condition that could be aggravated by the experimental intervention, or any condition judged by the physician (Dr. Halstead) as being unsuitable for respiratory training.
- has dysarthria or a language disorder
- has a hearing loss that is not adequately managed
- has a cognitive disorder that might affect treatment compliance
- is unable to give informed consent

Inclusion of Women

No subjects will be excluded based on gender. Based on published literature, treatment seeking patients with presbyphonia are generally equally divided between female and male. Thus, we estimate that approximately 50% of study participants will be female. No outreach program to recruit women is planned, because all patients with presbyphonia who meet inclusion criteria after undergoing a voice evaluation at the participating institution, regardless of gender, will be invited to participate. While no subjects will be excluded based on gender, it is highly likely that the majority of participant raters will be women as that is the current composition of speech-language pathologists.

Inclusion of Minorities

No subjects (patient or control subject groups) will be excluded based on race or ethnic origin. However, only English-speaking participants will be included in the study.

Gender, ethnic and racial information will be collected at the study enrollment. Ethnicity (i.e., Hispanic/Latino, Non-Hispanic/Latino) will be recorded separately from race. All applicable racial categories (i.e., American Indian/Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American, White) are recorded for each subject. All ethnic and racial totals will be reported, including specific categories for those individuals who report mixed racial descent. The Targeted/Planned Enrollment Tables for the participating institution are included in the Targeted/Planned Enrollment section, which indicate the anticipated ethnic and racial mixes of the subject sample. Numbers reflected in these tables parallel the ethnic and racial mixes of the service areas of the participating institution. No outreach program to recruit minorities is planned because all patients with presbyphonia who meet inclusion criteria after undergoing a voice evaluation at the participating institution, regardless of race or ethnic origin, will be invited to participate.

While no subjects will be excluded based on race/ethnicity, it is highly likely that all of the participant raters will be White Non-Hispanic as that is the current composition of speech-language pathologists.

Inclusion of Children

It has been well documented that infants and children differ significantly from adults in laryngeal, respiratory and neurological anatomy and physiology. Presbyphonia is a voice disorder caused by age-related changes in the laryngeal, respiratory and neurological systems, including muscle atrophy, changes in the vocal fold histology and in lung tissue and ribcage mobility. The aging process may differ between individuals, with symptoms of presbyphonia reported to occur as early as 50 years old. No case of presbyphonia has ever been reported in a child under 18 years old. The aim of this study is to assess the effects of respiratory training in patients with presbyphonia, therefore, the topic is not relevant to children. Although respiratory training could potentially be beneficial for treating other types of voice disorders, including those affecting children, a separate, age-specific study in children, would be warranted. Therefore, children are not a part of the current study.

6.0 Number of Subjects

Forty-eight patients-participants and up to six raters-participants will be recruited for the study.

7.0 Setting

Data Collection Site: All data collection and study activities will be conducted at the Medical University of South Carolina (MUSC). The patient subject sample will include 48 treatment-seeking patients diagnosed with presbyphonia at the Evelyn Trammell Institute for Voice and Swallowing (division of the Department of Otolaryngology-Head & Neck Surgery). The sample will be limited to the MUSC site because historical accruals have been shown sufficient to meet power (see participant section above). Further, the data quality and logistical challenges faced in multi-site trials go beyond the scope and expense of this current proposal. Participant raters will be recruited from SLPs who have an affiliation with MUSC and who have experience in working with voice patients.

8.0 Recruitment Methods

Following IRB approval, participants will be recruited from the treatment-seeking population at the Evelyn Trammell Institute for Voice and Swallowing (division of the Department of Otolaryngology-Head & Neck Surgery) - Medical University of South Carolina (MUSC). As part of usual care, all patients will undergo a videostroboscopic assessment conducted by the laryngologist, Dr. Halstead and will be referred to voice

therapy with a certified SLP to start usual treatment. Patients will undergo a brief screening interview by Dr. Halstead, after which qualifying patients will be offered participation in the study.

9.0 Consent Process

Interested and eligible patients will meet with a study team member shortly after being informed of the study (on the same day if possible). The consent process will take place in Rutledge Tower. The study member will provide a detailed description of the study and of its risks and benefits and the patient will be handed a written document with all the information. The study member will then discuss with the prospective participant and will ask specific questions to ensure a good understanding of key elements related to the study. Patients will be prompted to ask any questions they have. Finally, patients will be informed that their decision to participate or not in the study will not impact the care that they will receive at MUSC. Following this procedure, written consent will be obtained from interested participants. Following muscle pressure testing, participants whose muscle pressure results don't meet stratification requirements will be excluded from the study.

10.0 Study Design / Methods

Overview

After being enrolled in the study, treatment-seeking patients with a diagnosis of presbyphonia will undergo baseline respiratory assessments including spirometry and respiratory muscle strength measures as well as voice recordings (acoustic assessments). Participants will then be blocked-randomized (based on their MIP and MEP) to one of three groups using a 3-parallel arm design: (2 experimental groups and 1 control group), using a 3-parallel arm design: 1) inspiratory training (IMST) (experimental group), 2) expiratory training (EMST) (experimental group), or 3) standard of care (VFE) (control group), delivered four times (see table 1 for participant timeline). The sessions will occur on the same days as the participants' scheduled voice therapy sessions when possible. Participants will be asked to practice their respective exercises for 10 minutes, twice daily, seven days a week during the duration of the study. A final assessment session, after the 4th therapy session, will mirror the baseline measures. Participants will receive a monetary compensation of $20 for each study visit, for a maximum of $80 for the whole study. Payments will be made via cash. Outcomes that rely on subjective judgment (visual ratings of

videostroboscopy and perceptual judgments of voice quality) will be rated by trained judges (SLPs) blinded to the group assignment. [**Note**: Long-term follow-up will not be conducted. This study's focus is on the mechanistic effects of the intervention; future studies, given positive outcomes from this study, will explore the effectiveness and long-term effects.]

Table 1: Participant Timeline

Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
Baseline assessment session			
Therapy session **1**	Therapy session **2**	Therapy session **3**	Therapy session **4**
			Final assessment session

Patient Participants

Standard of Care Assessments (Procedures being performed already for diagnostic purposes)

- **Laryngeal imaging**: prior to the examination, the laryngologist will administer topical lidocaine and neosynepherine in a spray to one of the nasal cavities. The laryngologist then passes the camera through the nose to examine the vocal folds. The participant will be asked to sustain phonation on the vowel /i/ for at least 3 seconds and to repeat with pitch and loudness variations.
- **Acoustic Assessments**: The microphone is positioned at a 45˚ angle and at a standardized distance from the mouth of the participant. The participant is asked to sustain phonation on the vowel /a/ at a comfortable loudness for 3-5 seconds and as loud as possible for 2 seconds, and to glide to a high pitch and to a low pitch. They are then asked to read the 6 CAPE-V sentences and to have a

short natural conversation with the speech therapist. The participant is then asked to rate their perceived phonatory effort (PPE) on a scale.

- **Self-assessments**: The participant is asked to fill out the Voice Handicap Index questionnaire, the Reflux Symptom Index, and the Glottal Function Index.
- **Aerodynamic assessments**: The participant wears a face mask over the nose and mouth, which directs the air flow. A tube connected to a pressure transducer is passed through a hole in the mask, and inserted between the lips. The participant is asked to produce short utterances each comprised of minimally five /pi/ syllables at a rate approximating 1.5 - 2 syllables per second (/pi-pi-pi-pi-pi/). Each string of at least five syllables should be produced on one breath/exhalation. The task is repeated 3 times at comfortable pitch and loudness.

Standard of Care Intervention (Procedures being performed already for treatment purposes)

- **Vocal Function Exercises:** Participants in all 3 groups will be instructed to follow the 4 steps of the Vocal Function Exercises (VFE) protocol, developed by Stemple (2005) and commonly used by speech language pathologists (SLP) with voice patients: (a) sustain the vowel /i/ on the musical note F (above middle C for women; below middle C for men) for as long as possible. Repeat as judged by the SLP. (b) Glide from the lowest note to the highest note on the word "knoll". Repeat as judged by the SLP. (c) Glide from the highest note to the lowest note of the word "knoll". Repeat as judged by the SLP. (d) Sustain the notes C-D-E-F-G (starting from middle C for women and an octave below middle C for men) on the word "oll", for as long as possible. Each note will be repeated until the participant finds the right placement (forward-focused voice), as judged by the SLP. Humming exercises will be used to facilitate placement of the voice.
- Counseling and patient education during the therapy sessions.

Experimental Assessments (Procedures to be performed solely as part of this research study):

Firstly, the medical chart of the participant will be reviewed to obtain the following information: height and weight. This information will be used to perform the respiratory and muscle pressure assessments. The medical chart will also be used to track the speech therapy appointments, since research visits will take place on the same days. Spirometry assessments will take place at baseline and after the fourth intervention session. Muscle pressure testing and acoustic assessments will be conducted at baseline and before and after each intervention session.

- **Spirometry**: Prior to the tasks, the participant will put on a nose clip and make sure that the lips are well sealed around the tube with no air is escaping. They will be asked to breathe normally, and then take a full inspiration and blow out with force during at least 6 seconds, in the spirometer. Those maneuvers will be repeated at least three times, to verify test reliability. No more than eight repetitions should be needed(47). The participant is seated to reduce risks of fall.

- **Muscle pressure (maximum inspiratory pressure-MIP- and maximum expiratory pressure-MEP)**:

    - MIP: the participant is instructed to exhale slowly and completely, seal lips firmly around the mouthpiece, and then breathe in forcefully. The PI will note the largest negative pressure sustained for at least one second on the pressure gauge. The participant will rest for about one minute and then repeat the maneuver up to 4 additional times (with the goal of matching the highest 2 trials within 10 cmH_2O)(48).

    - MEP: the participant is instructed to inhale slowly and completely, seal lips firmly around the mouthpiece, and then breathe out forcefully. The PI will note the largest positive pressure sustained for at least one second on the pressure gauge. The participant will rest for about one minute and then repeat the maneuver up to 4 additional times (with the goal of matching the highest 2 trials within 10 cmH_2O) (48).

- **Acoustic assessment**: The microphone is positioned at a 45˚ angle and at a standardized distance from the mouth of the participant. The participant is asked to sustain phonation on the vowels /a/ and /i/ at a comfortable loudness for 3-5 seconds and as low and as loud as possible, to glide to a high pitch and to a low pitch, and from a soft voice to a loud voice. They are asked to sustain the vowel /a/ for as long as possible. They are then asked to read the 6 CAPE-V sentences and to have a short natural conversation with the speech therapist. The participant is then asked to rate their perceived phonatory effort (PPE) on a scale.

- **Self-Assessment questionnaire:** the participant will be asked to fill out the Communicative Participation Item bank (CPIB) questionnaire, which consists of 10 questions on communication.

Participants will be stratified based on their muscle pressure measures: 1) within normal limits MIP and MEP; 2) preserved MIP and decreased MEP; 3) preserved MEP and decreased MIP; 4) decreased MIP and MEP. This stratification is crucial to the study design because it will ensure an equal repartition of the

different respiratory profiles and deficits across treatment groups. Participants that don't meet stratification requirements will be excluded from the study.

Participants will be blocked-randomized into three groups (allocation ratio 1:1:1): IMST, EMST and VFE (see description of the interventions below).

Experimental Interventions (Procedures to be performed solely as part of this research study):

Participants in all groups will attend four sessions with a study team member. Intervention sessions will last approximately 30-45 minutes each. Each session will include pre- and post-treatment muscle pressure and acoustic measurements.

- **Inspiratory Training**: Inspiratory training will be conducted using an inspiratory pressure threshold trainer (Philips Respironics® Threshold IMT or POWERbreathe® Medic Plus, for patients with a MIP more than 83 cmH_20), which consists of a mouthpiece with a spring-loaded valve(25). The valve blocks the airflow until the threshold pressure achieved and allows airflow as long as the sufficient pressure is maintained. The threshold will be set at 75% of the participant's initial MIP, as reported in the literature with elderly participants(16). If it is too hard for the participant, the load will be lowered until the participant is able to perform the exercises. The load will be adjusted weekly by the study team member to maintain a threshold at 75% of the participant's MIP. Daily practices will consist of 5 sets of 5 breaths with the device with a break between sets, repeated twice daily (15, 18, 31).
- **Expiratory Training**: Expiratory training will be conducted using an expiratory pressure threshold trainer (EMST150) which consists of a mouthpiece with a spring-loaded valve. The valve blocks the airflow until the threshold pressure is produced (set at 75% of the participant's initial MEP, per literature with similar age groups(32-34)), and allows the airflow as long as the sufficient pressure is maintained. Participants will be asked to exhale forcefully into the mouthpiece after a full inspiration. If it is too hard for the participant, the load will be lowered until the participant is able to perform the exercises. The load will be adjusted weekly by the study team member to maintain a threshold at 75% of the participant's MEP. Daily practices will consist of 5 sets of 5 breaths with the device with a break between sets, twice daily(32-34).

Home Practice: Participants will be instructed to practice their respective exercises twice daily, and to log their practice in a compliance journal (days of training, perceived effects of treatment or other comments)

as well as to contact a research team member if any difficulty arise. In addition to in-person therapy sessions, weekly phone calls will clarify aspects of the training and encourage treatment adherence.

Rater Participants

Procedures that will be performed solely as part of this research study:

Raters will rate the audio recordings with the CAPE-V form and the videostroboscopy images with the VALI form. They will rate pre- and post-intervention de-identified recordings for each participant, and an additional sampling of 20% of the recordings (for intrarater reliability testing).

Data Collection

Data collected will be the same for Aim 1 and Aim 2. It will include information in the patient's medical record (obtained from standard of care assessment) and obtained through a demographic questionnaire as well as clinical data using standardized collection instruments: spirometry measures, muscle pressure measures and acoustic assessment.

Each video and audio recording will be de-identified when videos are converted into .mpg, .nsp or .mp3 files before distributing the recordings via Box for analysis. Participant raters will review the de-identified digitized recordings for the purposes of data collection and score each video and audio recording using the VALI and CAPE-V rating forms, respectively.

Spirometry, muscle pressure data, and voice data will be recorded in a data collection sheet by the study team member. Data collection sheets will be labeled with the alphanumeric identifier of the patient-participant. Completed data collection sheets, with ratings from the CAPE-V and VALI, will be entered in the database by a study team member. Research records will be retained for a period of six years to allow evaluation and repetition of the results by others.

Study personnel will enter mandatory data fields for demographics according to the NIH minimum standards for maintaining, collecting and presenting data on gender, race and ethnicity. The demographic and clinical data will be exported for analysis.

12.0 Data Management

Data Analysis Plan

Demographic characteristics will be compared across the 3 intervention groups, using a RxC contingency table method for categorical variables (gender, smoking history, voice use, racial and ethnic category) and a one-way ANOVA for continuous variables (age, weight, height). Baseline characteristics will be compared across the 3 intervention groups using a Kruskal-Wallis one-way analysis of variance by ranks for ordinal data (GFI, RSI, and VHI scores), a RxC contingency table for categorical variables (glottal gap shape, free edge contour, vertical level, phase closure) and a one-way ANOVA for continuous variables. **Aim 1**: To assess the effects of respiratory training on voice and respiratory outcomes in patients with presbyphonia. Data will be analyzed on an intention-to-treat basis using multifactor repeated measures generalized linear regression. Distributional assessment will be made for each outcome to confirm optimal distributional assignment and potential need for outcome transformation (i.e. log link). In the model, the repeated factor is time, which has two levels (pre- or post-intervention) and the independent factor is the intervention, which has three levels (IMST, EMST, VFE). In the case of a significant between-subjects effect, multiple comparison tests will be conducted to determine which groups differ. The post-hoc analysis will be done using Tukey's honestly significant difference (offering protection against type I error without being too conservative). Spearman and Person correlations will be calculated to establish inter and intra-rater reliability. **Aim 2**: To identify profiles of presbyphonic patients that would benefit the most from respiratory training. Logistic regression will be conducted to predict which patients improved following inspiratory training and which patients improved following expiratory training, based on their baseline clinical characteristics. Two outcome variables will be indicative of meaningful clinical improvement: 1) MPT (to measure function), and 2) GFI (to measure patient perception of function). Meaningful clinical improvement will be defined by an increase of at least 4 seconds in MPT or a decrease of at least 4 points in GFI score. Participants will be dichotomized as having meaningful clinical improvement, or not, based on these outcomes. Predictors will include MIP, MEP, maximum SPL, breaths per minute, FVC, FEV1, and P_s. These measures were chosen because they are directly influenced by the integrity of the respiratory system.

Sample Size Justification

We considered maximum phonation time (MPT) as the primary outcome measure for sample size calculation. This measure was chosen because 1) low MPT is a hallmark of patients with presbyphonia, and 2) MPT is directly affected by both the laryngeal and respiratory systems. To estimate the expected effect size between VFE and the I+IVFE and E+VFE groups, we considered MPT values from groups of an

elderly population with different glottal closure and spirometry profiles(49). Considering that a combined intervention (inspiratory or expiratory training combined with voice therapy) would address both laryngeal and respiratory deficits, and that a voice therapy-only intervention would directly address only the laryngeal deficits, we compared MPT between the no-deficit group (complete glottal closure and normal spirometry) and the respiratory-deficit group (complete glottal closure and altered spirometry)(49). Based on these values and the pooled standard deviations, the expected difference between our control and experimental groups would represent a large effect size. As for the within-subjects effect, a study by Nam et al.(50) found a 33% increase in MPT following a respiratory training intervention program in young adult singers. This corresponds to a very large within-subjects effect size with values of d exceeding 1.2. For Aim 2, we will assess improvement in 2 ways: function (a MPT increase of 4 seconds, which has been associated with a positive perceived effect following voice therapy in older adults(51)) and patient perception of function (a Glottal Function Index (GFI) score decrease of 4 points). An increase of 4 seconds in MPT and a decrease of 4 points on the GFI instrument both correspond to medium-large effect sizes considering the reported standard deviations of these measures in older subjects and in patients with glottal insufficiency (5.1 and 4.5, respectively) (42, 52). Based on the reported studies, the expected effect size for within-subjects and between-subjects differences was set at d=0.90. To have an 80% power to detect an effect size of d=0.90 with an alpha of 0.1 (since this is a pilot study), 15 participants are needed in each group. To account for loss to follow-up (estimated 10% dropouts rate), up to 16 participants will be recruited for each group, 48 patients total.

Based on estimated accrual rates, we calculated an average of one presbyphonic patient per week during the recruitment period of 16 months, for a total 64 participants. We are therefore confident of meeting our sample size goal.

Confidentiality

Protection against the loss of confidentiality will be diminished by 1) completing study aims at one data collection site, 2) minimizing the participants involved to only those needed to accomplish the study aims (see sample size justification above), 3) de-identifying data at the earliest opportunity, and 4) maintaining stored data in locked locations whose access is restricted to members of the study team and on the secure MUSC network.

All data will be entered into a database, linked, and de-identified, and labeled with an alphanumeric identifier. Further use of data will be de-identified. The link between patient identity and alphanumeric identifier will remain confidential in a study team member's locked office in a locked cabinet and on a password protected server (MUSC network). Electronic databases used for this study will be password protected and controlled by the study team. Only the study team will have access to participants' identities. Study staff not directly involved with the patient (e.g., biostatistician) will not have access to the linkage between identifier and subject-identifying information. Identities will be maintained in the general study research folders as identifiers on the signed informed consent forms, HIPPA forms, remuneration forms, and codebook. Once a participant is enrolled, he/she immediately will be identified by an alphanumeric code unrelated to any patient's protected health information. This code will effectively de-identify the participant and be used for unique participant data identification in all databases. Access to the electronic database will have a combination of physical and electronic security protections (firewalls) to prevent unauthorized access to this data. Appropriate back-up routines also will be performed to protect data integrity.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

A data and safety monitoring plan will be implemented by the PI to ensure that there are no changes in the risk/benefit ratio during the course of the study and that confidentiality of research data is maintained. Each member of the study team will meet with the PI and review confidentiality issues prior to having contact with research subjects.

The monitoring of adverse events will be ongoing throughout the study. Investigators and study personnel will meet regularly to discuss the study (study goals and modifications of those goals; participant recruitment and retention; progress in data coding and analysis; documentation, identification of adverse events or research participant complaints; violations of confidentiality) and address any issues or concerns at that time. Minutes will be kept for these meetings and will be maintained in the study regulatory folder. Any instances of adverse events will be immediately reported to MUSC's IRB using the standard forms and procedures that have been established by the IRB. The yearly IRB renewal for this study will include a summary report of the Data and Safety Monitoring Plan findings from the prior year.

Due to the minimal risk of the study, and because no serious adverse events are expected, there will be no specific safety endpoints. However, adverse events and unanticipated problems will be immediately reported. The laryngologist, will review adverse events and unanticipated problems and provide an expert assessment as to the probability of the event/problem being related to the experimental procedures. This will be determined mainly by the temporal relationship with the procedure, the environment, and the subject's clinical state.

14.0 Withdrawal of Subjects

In the cases where subject should develop a health condition non-related to the study protocol, a study team member would discuss with them that it is not appropriate at this time, given medical concerns, that they continue with the study intervention. The laryngologist, Dr. Halstead, would be informed of the situation and the medical team would make sure that the participant receives appropriate medical assistance.

Subjects are allowed to withdraw at any time, they are clearly advised that this will not affect their medical care or any aspects of their treatment.

15.0 Risks to Subjects

Potential Risks

Risks to subjects consist of 1) loss of confidentiality and 2) adverse events related to spirometry and muscle pressure testing 3) adverse events related to the experimental interventions (inspiratory and expiratory training) 4) incidental findings 5) risks associated with randomization and 6) unknown risks. There are no known risks are associated with acoustic assessment of voice.

Loss of confidentiality: The study will involve data collection from human subjects and is therefore subject to the risk of loss of confidentiality.

Spirometry and muscle pressure testing: Participants may feel the need to cough or may feel short of breath and/or dizzy during or after the test. There is a risk of syncope during the forced vital capacity (FVC) measurement.

Inspiratory training: Risks of discomfort, dizziness and light-headedness related to hyperventilation(53). The participant may feel short of breath or notice a pulse rate increase. Inspiratory training generates a

negative pressure in the thorax and for this reason it could aggravate conditions such as a pneumothorax, a middle ear pathology (such as a tympanic membrane rupture) or an acute unresolved sinusitis. Thus, patients with any diseases that are judged by the physician to be at risk of being exacerbated by the inspiratory training intervention will be excluded from study participation.

Expiratory training: During the expiratory training exercises, the patient has to generate sufficient expiratory effort to open a threshold valve and allow air to flow. The action increases the intraoral and intrathoracic pressures and has been compared to a sub-maximal Valsalva maneuver(54), which has been associated with blood pressure, heart rate changes and abnormal cardiac findings(55). However, expiratory training is not comparable to a typical Valsalva maneuver for two reasons: 1) the duration of the isometric muscle contraction during expiratory training is of approximately 2 seconds, which is much shorter than during a typical Valsalva maneuver (15-20 seconds)(54, 56); 2) during expiratory training, complete closure of the glottis rarely occurs, and when it does it is very briefly(54). Laciuga et al.(54) tested the effect of expiratory training on young health adults and found no acute changes in cardiovascular response (heart rate, blood pressure, oxygen saturation) and no adverse events following a session of 25 expiratory training trials. However, expiratory training is not recommended in older patients with certain cardiovascular disease or with untreated hypertension(18). Thus, patients with any diseases that are judged by the physician to put the patient at risk will be excluded from participating in this study.

Expiratory training is currently used in clinics and in research with various patient populations of the same age group as patients with presbyphonia, including patients with Parkinson's disease, multiple sclerosis and subacute stroke, as well as sedentary elderly participants (18, 30, 53, 57) . No serious adverse events have been reported in the literature. Nonetheless, it is suggested that patients be cleared by a physician before undergoing expiratory training. We will follow this recommendation.

Incidental findings: Spirometry and muscle pressure evaluations are screening tests and therefore no diagnosis will be made based on the patients' performance.

Risks associated with randomization: This study's goal is to test the effectiveness of two types of intervention (inspiratory training and expiratory training) and to compare them to usual care received by voice patients when working with SLPs (voice exercises only). There is a chance that undergoing respiratory training may be less effective than using the additional time to work on voice exercises.

Unknown risks: Respiratory training has never been tested on patients with presbyphonia. The results of this combination are unknown. Although unlikely, there is a slight risk that unforeseen adverse events could result from this combination.

Protections Against Risk

Loss of confidentiality: Protection against the loss of confidentiality will be diminished by 1) completing study aims at one data collection site, 2) minimizing the participants involved to only those needed to accomplish the study aims (see sample size justification above), 3) de-identifying data at the earliest opportunity, and 4) maintaining stored data in locked/password protected locations whose access is restricted to members of the study team. All data collection and study activities will be conducted at MUSC. The patient subject sample will include up to 48 patients referred for a videostroboscopy within the scope of their usual care at MUSC and who meet the inclusion criteria. The sample will be limited to the MUSC site because historical accruals have been shown sufficient to meet power (see participant section above). Six participant raters will be recruited from SLPs who have experience with voice disorders. An alphanumeric identifier will be used instead of patient participant name and rater participant name at the earliest possibility. In order to ensure participant's confidentiality, database entry will be password protected and study documents will be maintained in a locked cabinet in the PIs locked office. Patient identity will also be protected by confidentiality policies and procedures already in place at the MUSC site. A participant may withdraw from the study at any time without penalty or prejudice.

Spirometry and muscle pressure testing: If the patient-participant manifests signs of discomfort or dizziness, the spirometry or muscle pressure testing maneuver will be interrupted following the American Thoracic Society's (ATS) recommendations(47). Stopping the maneuver will avoid a syncope, which could follow due to the interruption of venous return to the thorax during prolonged exhalation. As a precaution, all assessments will be done in a sitting position, in a chair with arms and without wheels to prevent falls.

Respiratory training: Respiratory training will be done in a sitting position, in a chair with arms and without wheel to avoid falls in the case where the participant would feel dizzy or light-headed. Health screening by Dr. Halstead will be conducted to assess suitability for the training. To reduce risks of adverse events, patients that present with any pathology that would put them at risk when undergoing respiratory training will be excluded. This decision will be made by Dr. Halstead based on the patient's history and clinical evaluation.

During the study, patients will be asked to report and log in their journal any adverse events they are experiencing while conducting the respiratory training. Safety data will be monitored closely by the research team (see Data and Safety Monitory Plan) and a decision to stop treatment will be made if a participant presents with health concerns, as judged by the study team members and/or Dr. Halstead. In cases of slight discomforts, the participants will be invited to take a break from the training and to breathe normally until the discomfort passes before resuming the exercises.

Incidental findings: Spirometry and muscle pressure evaluations are screening tests and therefore no diagnosis will be made based on the patients' performance.

Risks associated with randomization: Prior to being enrolled in the study, the patient will be clearly advised of the risks associated with randomization and the possibility that he or she may not be randomized to an experimental group. Participants will also be warned that the experimental treatments may not be proven to be effective.

Unknown risks: Study data and adverse events will be closely monitored by study personnel throughout the study.

16.0 Potential Benefits to Subjects or Others

The experimental groups may benefit from receiving a respiratory training intervention. Respiratory training directly targets the respiratory system and *could* lead to greater improvements in both respiratory and voice outcomes than those observed with voice therapy alone.

There is a possibility that the participant will not directly benefit from being part of this research project.

For the subjects of the study, as well as for future voice patients who could benefit from this intervention if it were to be proven effective and to be implemented in common usual care, it could lead to important benefits:

- Improved respiratory and voice outcomes;
- Greater improvements in a person's daily activities involving communication;
- Reduced number of voice therapy sessions needed
- Improved voice-related quality of life

Because communication is a social activity, these benefits are also susceptible to impact the quality of life of the participants' significant other, family and caregiver.

The minimal risks associated with this research project are reasonable in relation to the potential benefits to the study participants and others. In the case where the intervention is not shown to be more efficacious than voice therapy only, the subjects would still receive the benefits from standard of care voice therapy.

Participant-raters will be compensated at a rate of $40 for every 10-rating package (one package includes an endoscopy recording and an audio file). It is estimated that each rater will rate a total of 39 packages, for a total of $160 for their participation in the study.

Both patient participants and participant raters may indirectly benefit, along with other patients, clinicians and society from the dissemination and implementation of the results of this research. The results of this research if in-line with our pilot data, will provide evidence that will serve as a guide for speech-language pathologists to inform patient management decisions. In general, any study that improves the effectiveness of voice intervention and the evidence upon which treatment recommendations are based may improve the health status and quality of life of patients and decrease the economic burden of voice disorders. These benefits outweigh the minimal risks that may result from loss of confidentiality and discomforts associated with the respiratory training interventions.

Importance of the Knowledge to be Gained

The paucity of evidence supporting the therapeutic benefit of respiratory training for patients with voice disorders is concerning considering their widespread use by speech language pathologists (SLPs) (58, 59). Despite the well documented relationship between the respiratory and laryngeal systems, **evidence-based guidelines for respiratory training are non-existent in the field of voice therapy. This void represents a critical barrier to optimal care for patients with voice disorders, especially for patients with presbyphonia who have known respiratory declines due to aging**.

Current breathing exercises used by SLPs, such as diaphragmatic breathing, increasing extent of thoracic expansion, and increasing period of expiratory airflow on phonemes /s, z, a, æ, i/(29, 60) have not been tested in clinical trials with voice patients. It is likely that most of these exercises are not adequately intensive, in terms of loading, to induce neuromuscular and hypertrophic changes necessary for improving

respiratory muscle strength. Despite this lack of evidence, many clinicians devote substantial time in their therapy sessions to these 'breathing exercises'. **In-person therapy time with a SLP is already limited and therefore should not be spent on subthreshold 'breathing exercises', such as diaphragmatic breathing, that lack evidence**. If respiratory training does improve function, it would give clinicians an alternative modality to substitute for less evidenced 'exercises' and change current practice by encouraging SLPs to administer an evidence-based respiratory training. In addition, results from this study would allow to identify profiles of patients likely to benefit from respiratory and more precisely from inspiratory or expiratory training, further promoting efficient and impairment-specific allocation of therapy time.

Conversely, negative findings from this study would raise questions about the relevance of respiratory training in patients with presbyphonia and help focus research as well as clinical practice on more effective treatment approaches. **If adequately rigorous respiratory training does not produce sufficient improvement in vocal function, it would be a mandate to stop wasting treatment time on subthreshold 'breathing exercises'.**

17.0 Sharing of Results with Subjects

During the course of the experimental sessions, the study team member will discuss the evolution of the respiratory outcomes with the participant. At the conclusion of the study, a study team member will offer to send an email to interested participants, with the findings from the study.

18.0 Drugs or Devices

New inspiratory and expiratory muscle trainers will be stored in the locked office of a study team member. The team member will bring the appropriate device (inspiratory or expiratory trainer) to the participant's first therapy session. The participant will be given the device for personal use (home practices), and therefore will go back home with the device. The participant will be instructed how to use and clean the device and will be reminded to bring it at every therapy session.

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