Official Title: Preliminary Studies to Test the Effects of Ambulatory Voice Biofeedback
NCT Number: 03416829
Date: June 16th, 2022

Study Protocol:
Study One will assess if AVB paradigms can effect short- and long-term changes in vocal loudness behavior in a small group of patients with vocal hyperfunction (VH). More specifically, it will determine which of three types of ambulatory feedback results in better learning/retention (100% frequency, 25% frequency, or delayed summary feedback every 2 minutes of voicing) of a new vocal behavior (reduced vocal loudness) in three groups of 15 patients with vocal fold nodules. It is hypothesized that patients receiving lower frequency or summary feedback will produce lower initial performance but higher short- and long-term retention than patients receiving feedback 100% of the time.

Inclusion/Exclusion criteria for the patients are summarized below:

Inclusion Criteria	Exclusion Criteria
Age: 18 – 65 years Previous monitoring: Patients must have successfully completed approximately 1 week of baseline voice monitoring in protocol 2011P002376 For Study 1 only: Diagnosis: vocal fold nodules	Non-English Speaker Unable to answer questions and/or follow instructions Patients with a sensitivity to hypo allergenic adhesive Pregnant women

Study One will include 54 total patients with phonotraumatic VH (45 patients + potential 20% dropout rate) and will be recruited from the Massachusetts General Hospital (MGH) Voice Center. The procedures and design for Study One are essentially identical to a previously approved IRB protocol (# 2014001870) which used normal subjects [37]. The proposed study seeks to replicate the previous results in patients with VH in order to move toward the clinical implementation of this approach. Each subject will be assigned (via block randomization) to three groups with different AVB schedules: 1) 100% immediate biofeedback (vibrotactile cueing every time the participant exceeds a vocal intensity threshold), 2) 25% immediate biofeedback (vibrotactile cueing every 4th time the participant exceeds a vocal intensity threshold), and 3) delayed summary biofeedback (no cueing; summary statistics shown every 2 minutes of voiced time). Patients with phonotraumatic VH have been chosen since reducing vocal loudness is often a goal of therapy.

All patients will be recruited following completion of Partners approved protocol 2011P002376. If a subject has not successfully completed monitoring during protocol 2011P002376, s/he will not be eligible for enrollment into this study. The patient's pre-therapy ambulatory monitoring from protocol 2011P002376 will provide a baseline for deriving each patient's vocal intensity biofeedback threshold. The overall design of the study will be three days: Two days of consecutive monitoring—a day of AVB (Day 1) and a subsequent day of ambulatory monitoring without AVB to assess if the desired vocal behavior is retained (Day 2). Seven days after Day 1, patients will wear the monitor again without AVB to assess any long-term retention of the desired vocal behavior (Day 3). As there is typically a 3-4 week waiting period for beginning voice therapy at the MGH Voice Center, it is reasonable to assume that patients will have the required number of weeks available for this protocol before therapy commences.

TABLE I. Study 1 time points and associated visits/procedures.

Time Point One (Day 1)

Visit to MGH Voice Center

1. Investigator places VHM, marks the subject's neck at location of sensor, programs VHM for subject's biofeedback, starts recording.
2. Investigator will teach subject how to use VHM and respond to biofeedback

Recording of voicing in daily life

1. Subject will wear device and receive feedback on how loud s/he talks
2. Recording will automatically stop after 42 minutes of phonation (approx. 7-10 hours)
3. Subject will contact investigators to return device same day or charge device over night.

Time Point 2 (Day 2)

Visit to MGH Voice Center

1. Investigator places VHM, marks subject's neck at location of sensor, programs VHM, starts recording
2. Investigator will review with subject how to use VHM

Recording of voicing in daily life

1. Subject will wear device with no feedback
2. Recording will automatically stop after 42 minutes of phonation (approx. 7-10 hours)
3. Subject will contact investigators to return device same day or charge device over night.

Time Point 3 (Day 3)

Visit to MGH Voice Center

1. Investigator places VHM, marks subject's neck at location of sensor, programs VHM, starts recording
2. Investigator will review with subject how to use VHM

Recording of voicing in daily life

1. Subject will wear device with no feedback
2. Recording will automatically stop after 42 minutes of phonation (approx. 7-10 hours)
3. Subject will contact investigators to return device same day or charge device over night.

During biofeedback days, the VHM will only monitor the first 50,000 voiced frames—which are approximately 42 minutes of phonation ("frame" = 50 ms)—to ensure that each patient gets an equal opportunity to experience biofeedback. At typical phonation times of less than 10%, 42 minutes of phonation is achieved within 7-9 hours of monitoring time, which is an attainable goal for all patients.

The biofeedback threshold will be set at the 85th percentile of the patient's baseline (weeklong) vocal intensity histogram and the patients will be provided biofeedback to reduce the upper 15 % of their vocal intensity distribution (dB). More specifically, the VHM will provide a 250 ms vibrotactile cue via a smartwatch—see Figure 2(c)—every frame (100% frequency) or every 4th frame (25% frequency) the amplitude exceeds the biofeedback threshold. Those in the summary feedback group will receive a vibrotactile cue on their smartwatch after every 2 minutes of voiced time to alert them that their summary statistics are ready to be viewed. To ensure that the patient looks at the summary statistics in a timely manner and accurately understands their scores, multiple screens for user-interaction will be provided (they must indicate the correct score) and patient responses will be recorded in a text document.

The study endpoint will be achieved after satisfactory recording of 1 biofeedback day and two post-biofeedback days (3 total days).

Statistical Analysis Plan:

Study One will use a series of two 3 (Group) X 4 (Day - baseline, biofeedback, short- and long-term retention) mixed between/within ANOVAs will be conducted for the outcome variables Δ dB and overall percentage compliance. The findings of interest are the main effects of "Day" and the interaction effects of Group X Day. While appropriate post hoc tests will be conducted on the main effects (if significance is achieved), univariate follow-up tests, and if required, appropriate post hoc tests will be performed on the interaction effects. Results from our preliminary research [6] produced large effect sizes ($\eta 2 \approx 0.90$) between the biofeedback and non-biofeedback/baseline time periods. Furthermore, both limb and head/neck motor learning studies have demonstrated large effect sizes ($\eta 2 = 0.70–0.95$) between different feedback groups (decreasing frequency [10, 13-21, 49, 50] or delayed summary [10, 22-30, 51-53] feedback). Based on the

lower effect size ($\eta 2 = 0.70$) and the experimental design, power analysis indicated a sample of 14 participants per group with 80% power and alpha of 0.05. Since there are three experimental groups in Study One, the total sample size would need to be higher than 42 participants