INTRODUCTION

Paradoxical vocal fold motion disorder (PVFMD) is a disease process defined by inappropriate adduction of the vocal folds during the respiratory cycle, leading to symptoms of dyspnea.1–6 The symptoms are often acute in nature and can be quite variable in intensity and duration. Patients often describe a sense of laryngeal tightness or strangulation that is associated with cough, dysphonia, stridor, and dyspnea.1–4 PVFMD can occur with other respiratory disorders and often mimics asthma.1–4 In a review by Patel et al., the median time to diagnosis of PVFMD was 4.5 years because patients are often misdiagnosed with asthma and inappropriately treated with various medication trials.1 Patients with severe symptoms may present to the emergency department in respiratory distress; they often receive bronchodilators, intravenous corticosteroids, and benzodiazepines—or undergo airway interventions such as endotracheal intubation and tracheostomy.

The diagnosis of PVFMD is based on history and visualization of the larynx and upper airway in the awake patient during flexible fiberoptic laryngoscopy.2,5,6 Vocal fold immobility and other fixed obstructions of the airway must be ruled out in order to diagnose PVFMD. Vocal fold paralysis, glottic stenosis, subglottic or tracheal stenosis, tracheomalacia, laryngeal dystonia, and upper airway mass/lesion may have similar presentations to PVFMD and must be considered in the differential diagnosis.2,4,6 The treatment of concurrent inflammatory and psychogenic disorders is imperative because untreated conditions such as asthma, allergy, gastroesophageal reflux, anxiety, and panic disorder may exacerbate PVFMD symptoms.2 Previous reports have demonstrated improvement and resolution of dyspnea in 65% to 100% of patients when laryngeal control therapy and respiratory retraining protocols are instituted with speech language pathology.2,4,6

For persistent symptoms of dyspnea, patients undergo biofeedback therapy sessions with speech language pathology, for which visualization of their larynx and vocal folds via videolaryngoscopy can aid the patient in developing muscle memory and eliminating inappropriate adduction of the vocal folds during the respiratory cycle.6 Biofeedback techniques allow patients to better understand the biologic foundation of their laryngeal sensation and thus better prevent the inadvertent constriction of their vocal folds. These biofeedback sessions can
be performed with patients at rest or with symptoms of dyspnea following exertion.6

A small subset of patients with PVFMD have persistent dyspnea symptoms despite traditional laryngeal control therapy protocols and biofeedback sessions. It is not well understood which patients will fail these therapeutic interventions because there are so few overall. In addition, these patients have limited options for treatment when they fail therapy. For patients who have severe symptoms of dyspnea or refractory PVFMD after all other traditional therapeutic techniques have been trialed, the use of botulinum toxin injection to the vocal folds has been described as a treatment option.3,7–12 Brin and Altman both described the use of botulinum toxin injection for PVFMD, but those reports included patients with concurrent head and neck or other laryngeal dystonia.3,7 The objective of this study is to demonstrate the efficacy of vocal fold botulinum toxin injection therapy in patients who have refractory PVFMD without other forms of dystonia.

MATERIALS AND METHODS

After obtaining approval by the institutional review board, a retrospective chart review was performed of patients who underwent vocal fold botulinum toxin injection therapy for dyspnea in the setting of refractory PVFMD from July 2008 to January 2018. Prior to injection therapy, all patients underwent flexible fiberoptic videolaryngoscopy during initial assessment and exhibited signs of vocal fold adduction during respiration, leading to a diagnosis of PVFMD as defined by previously published protocols.2,5,6 Patients then underwent laryngeal control therapy with speech language pathology. Patients were determined to have persistent PVFMD symptoms when they experienced continued dyspnea, despite trialing all forms of rescue breathing and respiratory retraining techniques during in-office therapy with a speech language pathologist. At this point, biofeedback sessions were completed when the patient had persistent dyspnea. During these sessions, the patients underwent a repeat flexible fiberoptic videolaryngoscopy and practiced respiratory retraining techniques while visualizing the activity of their vocal folds and larynx on the video monitor. Refractory PVFMD was then diagnosed when patients had persistent dyspnea not attributable to other medical disorders and had exhausted therapeutic breathing techniques via laryngeal control therapy and biofeedback sessions with speech language pathology.

Once refractory PVFMD was diagnosed, office-based vocal fold botulinum toxin injections were offered and performed by a fellowship-trained laryngologist via a transcroicothyroid membrane, electromyography-guided approach. Initial injections were performed bilaterally with a starting dose of two units to both thyroarytenoid muscles. A repeat injection to the thyroarytenoid muscles only was offered at a 3-month time interval if the patient had improvement in dyspnea symptoms but recurrence of dyspnea at follow-up examination. The dosage was titrated based on degree and duration of improvement in dyspnea and presence and severity of any voice-related side effects.

RESULTS

Thirteen patients (9 female and 4 male) underwent vocal fold thyroarytenoid muscle botulinum toxin injection for refractory PVFMD from July 2008 to January 2018. The mean age was 40.69 years, with a range of 16 to 73 years (Table I). The patients were followed for an average of 24.8 months following initial injection, with a range of 5 to 69 months. The mean dose was 2.55 units per vocal fold (range 1.75–5.5 units). The mean number of injections was 3.85 (range 1–12 injections). Eleven of 13 (84.6%) patients experienced improvement in dyspnea, with two of 11 (18.2%) having complete resolution of symptoms following one injection. The two patients who...
did not have improvement in symptoms following botulinum toxin injection therapy eventually underwent tracheostomy due to severe symptoms leading to repeated emergency room visits, endotracheal intubations, and intensive care unit admissions. Both patients had improvement in dyspnea following tracheostomy, resulting in a documented decrease in emergency room visits and hospital admissions. Prior to tracheostomy, one patient had an increase in botulinum toxin dose twice before progressing to surgical intervention. These subsequent injections were performed to the thyroarytenoid muscles only. The second tracheostomy patient underwent one botulinum toxin injection and then eventual tracheostomy 3 months later due to persistent dyspnea and repeated hospital admissions during that time interval.

There was a statistically significant improvement in DSI scores; the mean preinjection DSI was 30.43 and improved to 17.43 postinjection ($P = 0.017$). Pre- and postinjection DSI scores were only available in eight of 13 patients because this scale became a standard part of assessment following its validation in 2014. All patients tolerated injection therapy well in the office-based setting. Temporary breathy voice quality was experienced by all patients, and this ranged from 3 to 14 days. The breathy voice quality led to a reduction in botulinum toxin injection dose in one patient. There were no other acute or long-term adverse side effects.

**DISCUSSION**

Dyspnea symptoms that result from PVFMD can be severe and long-standing prior to proper diagnosis. Patients have often seen physicians in multiple specialties, including primary care, emergency medicine, otolaryngology, pulmonary, allergy, neurology, cardiology, and gastroenterology, because the symptoms can overlap with many other disease processes. All these evaluations lead to significant healthcare utilization and medication trials that may be unnecessary in some instances. Diagnosis of PVFMD often leads to a reduction in medication use and emergency department visits while improving dyspnea and quality of life. Despite most patients experiencing relief of symptoms with laryngeal control therapy, there is a small subset of patients with severe or refractory PVFMD who remain difficult to treat.

There is a paucity of literature on how to best treat patients with refractory PVFMD. Benzodiazepines and heliox therapy can be helpful in acute settings but do not provide long-lasting relief of dyspnea, and patients often return to the emergency department for recurrent acute exacerbations. These severe attacks of dyspnea may lead to invasive airway interventions such as bronchoscopy, endotracheal intubation, and tracheostomy.

Vocal fold botulinum toxin injection has been described as a treatment option for refractory PVFMD symptoms. Most of the reports demonstrating efficacy of vocal fold botulinum toxin injection for dyspnea have been single-patient case studies. There has not been a standardized approach or treatment regimen reported to guide clinicians on best care for patients with refractory PVFMD. Goldstein et al. described a patient with severe PVFMD with partial improvement in symptoms following injection of 10 units of botulinum toxin to both thyroarytenoid muscles and 2.5 units to both false vocal folds. However, this symptomatic improvement was not long-standing, and the patient eventually underwent tracheostomy. Montijo et al. presented a pediatric patient who had complete relief of dyspnea for 6 months following botulinum toxin injection of 7 units to each vocal fold. They repeated the injection when symptoms recurred, and the patient had similar improvement in dyspnea lasting 5 months at last report.

There are no large case series or prospective studies reviewing the outcomes of patients treated with vocal fold botulinum toxin injection for refractory PVFMD. One series by Brin et al. originally reported the use of botulinum toxin injection to the vocal folds for dyspnea; four of seven patients experienced relief of dyspnea, but this series included five patients with a concurrent diagnosis of dystonia. Altman et al. reported on vocal fold botulinum toxin injection in five patients with PVFMD severe enough to require endotracheal intubation or tracheostomy, but again included two patients with concurrent dystonia. Given the well understood response of dystonia to vocal fold botulinum toxin injection, the results in these series may not appropriately represent the patient with refractory PVFMD without comorbid dystonia.

Our objectives were to present a larger case series of patients with refractory PVFMD and demonstrate the efficacy of bilateral vocal fold botulinum toxin injection for relief of dyspnea. Utilization of a validated survey such as the DSI aids in quantifying the improvement that patients experience following these injections. With a mean dosage of 2.55 units per vocal fold, patients are able to achieve improvement or resolution of their dyspnea with a smaller botulinum toxin dose than reported in smaller case series and single-patient reports. These smaller dosages likely result in fewer side effects and improved patient tolerance.

This case series did have two patients with complete resolution of dyspnea after one vocal fold injection of botulinum toxin. One theory for this resolution of symptoms is that the patient has a new baseline for their breathing and is able to more effectively utilize laryngeal control techniques going forward. Continued practice with laryngeal control therapy techniques is encouraged for these patients and may lead to better outcomes following the vocal fold botulinum toxin injection. It is also possible that these patients experience a placebo effect from the botulinum toxin injection, a possibility that applies to all patients studied here.

There are a few weaknesses of this study founded on the retrospective design and small sample size. We only had pre- and postinjection DSI results on eight of 13 patients because this validated scale became a standard part of clinic documentation in 2014. In addition, PVFMD is a highly variable disorder in its presentation and severity of symptoms, further complicating the ability to make standardized recommendations for how to best treat a small subset of refractory PVFMD patients. Regardless of these deficiencies, the majority of patients
with severe dyspnea symptoms and refractory PVFMD had improvement or resolution of their dyspnea following vocal fold botulinum toxin injection.

CONCLUSION
Vocal fold botulinum toxin injection is an effective treatment option for PVFMD and should be considered in patients with refractory dyspnea following appropriate medical therapy and respiratory retraining protocols. Refractory PVFMD is a rare entity and should only be diagnosed when all laryngeal control therapeutic techniques and biofeedback options have been trialed.

BIBLIOGRAPHY