EXERCISE-INDUCED EPISODIC LARYNGEAL BREATHING DISORDERS: CLINICAL FEATURES AND MECHANISMS

by

Adrianna C. Shembel

Bachelor of Science, The Pennsylvania State University, 2005

Masters of Arts, The University of Pittsburgh, 2008

Submitted to the Graduate Faculty of

The School of Health and Rehabilitation Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

SCHOOL OF HEALTH AND REHABILITATION SCIENCES

This dissertation was presented

by

Adrianna C. Shembel

It was defended on

November 15, 2017

and approved by

James Coyle, PhD, CCC-SLP, BCS-S
Professor, Department of Communication Science and Disorders
School of Health and Rehabilitation Sciences, University of Pittsburgh

Jessie VanSwearingen, Ph.D., PT, FAPTA
Associate Professor, Department of Physical Therapy
School of Health and Rehabilitation Sciences, University of Pittsburgh

J. Scott Yaruss, PhD, CCC-SLP
Professor, Department of Communicative Science and Disorders
College of Communication Arts and Sciences, Michigan State University

Committee co-Chairs/Dissertation Advisors:
Katherine Verdolini Abbott, PhD, CCC-SLP
Professor, Department of Communication Science and Disorders
University of Delaware

Susan Shaiman, PhD, CCC-SLP
Associate Professor, Department of Communication Science and Disorders

EXERCISE-INDUCED EPISODIC LARYNGEAL BREATHING DISORDERS: CLINICAL FEATURES AND MECHANISMS

Adrianna C. Shembel, PhD

University of Pittsburgh, 2017

Introduction: Exercise-induced episodic laryngeal breathing disorders (E-ELBD) are frequently misdiagnosed, leading to protracted periods of mismanagement (Bernstein, 2014; Traister, Fajt, & Petrov, 2016). These shortcomings are due to gaps in differential diagnosis of ELBD. A poor understanding of underlying mechanisms driving clinical expression further complicates ELBD management. Therefore, objectives of the proposed dissertation study were to (1) identify clinical benchmarks indicative of E-ELBD and (2) investigate two potential mechanisms driving E-ELBD: autonomic imbalance and stress reactivity (temperament).

Methods: 13 adolescent athletes with E-ELBD and 14 athletic volunteers participated in an exercise challenge and simultaneous flexible laryngoscopy. Participants were asked to rate their symptoms at rest and exercise from a list of symptoms associated with ELBD using a visual analog scale. Participants were then asked to complete the Early Adolescent Temperament Questionnaire (EATQ-R) Fear Subscale to measure perceived stress reactivity. Cardiovascular measures were taken throughout the protocol to evaluate autonomic responses. Glottal configuration and supraglottic responses at rest and exercise were analyzed post hoc using recorded endoscopic videos.

Results: Statistical differences between group and condition were seen with dyspnea severity and glottal configuration ($p < .05$). Other clinical features prevalent in the E-ELBD cohort—arytenoid prolapse, throat tightness, and stridor—were variably present amongst individuals with and without E-ELBD. Smaller sympathetic responses to vigorous exercise and faster parasympathetic reactivation post-exertion were observed in the E-ELBD group compared to controls. However, differences were not statistically significant ($p > 0.05$). Finally, responses on the Fear Subscale of the EATQ-R showed stress reactivity to be similar between the two groups, with significant differences between the athletes and the general adolescent population ($p < .001$).

Conclusion: Results showed inspiratory glottal configuration (> 8° adduction) and dyspnea (> 30/100 on VAS) with provocation to be good diagnostic indicators of E-ELBD. Blunted expiratory abduction responses in the E-ELBD group (< 32° abduction) suggests respiratory compensation. Sympathovagal balance may play a role in E-ELBD and should be further investigated. Caution should be exercised when extrapolating the role of temperament in E-ELBD pathogenesis. Outcomes can improve clinical management and sensitivity of inclusionary criteria for future studies.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

What a marathon this dissertation has been! As I take a moment sit back and *breathe,* I reflect on all the amazing people who have helped make this journey a success. You have all *inspired* me personally and professionally (okay, I promise I'll stop with the breathing puns!). I have so many "thanks" to give. Kittie, thank you for teaching me to see the bigger picture in research (and life!), for showing me the fun in taking greater risks, and for instilling in me the confidence to be an independent thinker. Sue, thank you for being my academic fairy godmother. I am eternally grateful for your guidance and mentorship and aspire to instill half your love and passion for speech-language pathology to future students. Jessie, I will miss our autonomic nervous system geek-out sessions! Thank you for your never-ending willingness to listen to me talk through musculoskeletal and neuromuscular concepts and for encouraging me to broaden my horizons outside the world of speech-language pathology. Jim, thank you for teaching me there is almost always an alternative theory and that often "it depends!" Scott, thank you for showing me the important role psychology plays in the field of speech-language pathology and the significance of not discrediting conditions as "it's all in your head."

To my MEEI family: Chris, thank you for your patience with me, for always being there, with a big smile and calming words of encouragement, and—most importantly—for making the study at Mass Eye and Ear a reality! Glenn, thank you for taking a chance on me and the study, as unconventional as it might have been! You immediately made me feel like part of the Mass Eye and Ear family, and for that I am eternally grateful. Cathie, thank you for your confidence, encouragement, and amazing clinical expertise. Section 6.3.2.1 is dedicated to you! Ziegillou, thank you for letting me bounce ideas off you and for all your words of wisdom and support over

the years. Doug, thank you for showing me not to take things too seriously, to laugh more, and to make the most out of life! Carolyn, thank you for being my monthly PVFM-phone buddy. Your guidance was crucial in helping me see the "forest through the *breathe*" (sorry, had to do it just *one* more time!). To all the raters who stared at countless larynges—Tom Carroll, Doug Roth, Christina Dastolfo-Hromack, Victoria McKenna, Maxine Van Doren, Cathie Ballif, and Jordan Piel—you helped make this study a reality. I owe you all a drink (or a few!). And to Manuel, without your MATLAB expertise, there would have been no laryngeal analysis! I owe you a drink and a night of Latin dancing!

To the Sacher family: Cha, you vowed you'd always be there to "scrape me off those proverbial (and actual!) marathon finish lines." And that you did. I would not be standing at this dissertation finish line today without all your cheering, words of encouragement, and support, especially during those times "lizard brain" set in. You deserve a finisher medal for putting up with me. Nancy and Rachob, thank you for believing in me, for helping me find more self-compassion, and for keeping it real. They say "it takes a village." I feel so incredibly lucky to be part of it.

Last, but not least, this work could not have been done without the generous financial support from the NIDCD NIH (1F31DC015752-01A1), University of Pittsburgh SHRS Audrey Holland Award, and the University of Pittsburgh SHRS Research Development Fund. I hope to one day pay it forward!

1.0 INTRODUCTION

Breathing is central to survival. We breathe for ventilation (gas exchange) as well as for voicing, speech, and smell (CliftonSmith & Rowley, 2011; van Dixhoorn, 1994). Dysfunctional breathing patterns can affect any of these tasks. *Episodic laryngeal breathing disorders* (ELBD) are one example of dysfunctional breathing. The term ELBD defines a spectrum of functional respiratory disorders thought to originate in the larynx (Christopher et al., 1983; Hoyte, 2013; Shembel, Sandage, & Verdolini Abbott, 2017). The predominant symptom is considered to be dyspnea resulting from dynamic laryngeal airway obstruction. In ELBD, these dyspneic symptoms are episodic, with sudden onset believed to be triggered by sensory, mechanical, or psychological stimuli (Christopher & Morris, 2010). Symptoms can be alarming and frightening, with considerable adverse effects on quality of life, work or school productivity, and social interactions (Mathers-Schmidt, 2001). Terms used to describe this spectrum of conditions include paradoxical vocal fold motion disorder (PVFMD), vocal cord dysfunction (VCD), inter-arytenoid region prolapse (IARP), irritable larynx syndrome (ILS), and more than 90 additional terms to denote pathology based on aberrant laryngeal-respiratory kinematics (Shembel et al., 2017) (see *Appendix A: Episodic Laryngeal Breathing Disorders Nomenclature* for list of terms). ELBD are most likely not a single disease process, but a *composite* of syndromes with as much overlap as there is differentiation in their features and mechanisms. Although dyspnea and atypical laryngeal

movement are considered axiomatic to the condition, the degree to which signs and symptoms present, how they manifest, and the triggers that induce these events can differ across individuals.

1.1 STATEMENT OF PROBLEM

ELBD encompass a heterogeneous spectrum of clinical features. Manifestations involve different symptom complaints, laryngoscopic findings, and trigger stimuli that induce episodes. In fact, over 200 observations of ELBD have been described across various bodies of literature within the last 140 years (Maat et al., 2011). However, efforts to organize and systematize these features have been sparse. This lack of unification has led to unclear diagnostic criteria, which has further resulted in diagnostic approaches based on exclusion (e.g., cardiopulmonary workup), misdiagnoses (e.g., asthma), and mismanagement (e.g., tracheotomy and intubation) (Ibrahim, Gheriani, Almohamed, & Raza, 2007). To further complicate matters, symptoms of ELBD both mimic and can co-occur with other conditions such as asthma, anxiety disorders, muscle tension dysphonia, and allergies (Ayres & Mansur, 2011; Benninger, Parsons, & Mastronarde, 2011; Campainha et al., 2012; Caraon & O'toole, 1991; Chiang et al., 2008; Christopher et al., 1983; Holmes et al., 2009; Jain et al., 2006; Kenn & Hess, 2008; Kivity et al., 1986; Low et al., 2011; MacConnell, Danielsen, & Symington, 2014; Martin et al., 1987; McFadden & Zawadski, 1996; Mokoka et al., 2013; Newman & Dubester, 1994; Niggemann et al., 1998; Parsons et al., 2010; Sokol, 1993; Tonini et al., 2009; Vertigan et al., 2008; Yelken et al., 2009). Therefore, differentiating symptoms specific to ELBD from other conditions can be challenging. In addition

to the lack of standardized methods to identify ELBD, there is also poor understanding of underlying mechanisms driving its manifestations.

1.2 SIGNIFICANCE OF WORK

In sum, gaps in the understanding of ELBD include (1) lack of systematic criteria to identify and categorize ELBD pathology, (2) dearth of physiological and pathophysiological comparisons between those affected and those without the condition, and (3) poor understanding of underlying pathophysiological mechanisms. These gaps have hampered our ability to accurately diagnose and treat individuals with ELBD. The focus in this work is on athletic adolescents with exercise-induced ELBD (herein referred to as E-ELBD, except for manuscript Chapters 4 & 5, which will use exercise-induced paradoxical vocal fold motion disorder [E-PVFM] due to familiarity issues). E-ELBD is thought to occur in 3-10% of athletes, typically in those who are young and competitive in their athleticism (Abu-Hasan, Tannous, & Weinberger, 2005; Backer, 2010; Brugman, 2003; Christensen et al., 2011; Christensen et al., 2010; De Guzman V et al., 2014; Heimdal, Roksund, Halvorsen, Skadberg, & Olofsson, 2006; Johansson et al., 2015; Landwehr, Wood II, Blager, & Milgrom, 1996; Maat et al., 2007; Nielsen et al., 2013; Nielsen, Hull, & Backer, 2013; Olin et al., 2014; Rundell & Spiering, 2003). However, it is unclear whether there is truly a higher prevalence of E-ELBD in competitive, young athletes, compared to the general adolescent population, or if this cohort is more likely to seek medical care due to the burdens E-ELBD imposes on their quality of life (Wiese-Bjornstal, 2010). Recent literature suggests, however, that athletes may be at a

greater risk of developing breathing problems (11-50%),[1] compared to the general population (10-12%). The thought is this higher prevalence may be related to increased exposure to cold, dry environments, or to pollen and pollutants during training periods. These influences can have synergistic effects with high physical loads and environmental exposure (Medelli, Lounana, Messan, Menuet, & Petitjean, 2006), although this theory is currently speculative.

Because symptoms mimic exercise-induced asthma, athletes with E-ELBD are often misdiagnosed as such and are administered high doses of inhaled corticosteroids or prednisone as a first line approach (Abu-Hasan et al., 2005; Bernstein, 2014; De Guzman V et al., 2014; Landwehr et al., 1996; Powell et al., 2000). Repercussions of this irrelevant pharmacological intervention can involve serious long-lasting iatrogenic consequences including osteoporosis, obesity, stunted growth, Cushing's disease, and hypertension (Christopher et al., 1983; Heinle, Linton, & Chidekel, 2003; Nahmias, Tansey, & Karetzky, 1994; Newman, Mason, & Schmaling, 1995; Noyes & Kemp, 2007; Sokol, 1993)**.** Protracted mismanagement also has psychological consequences including impairments to self-concept, feelings of isolation, and withdrawal from sports and the sports community altogether (De Guzman et al., 2014; Røksund et al., 2009; Weinberg & Gould, 2011).

[1] Asthma being the most common breathing condition.

1.3 DESCRIPTION OF CHAPTER STRUCTURE

The goal of this dissertation was to address gaps in knowledge of how we understand and recognize E-ELBD clinical presentation and pathogenesis as a means to better manage the condition. This work is part of a programmatic line of study to systematically identify biomarkers for ELBD subgroups, and to better understand pathophysiological mechanisms driving clinical expression across the ELBD spectrum. Chapter 2 is an overview of current knowledge in the domain of ELBD across the condition complex, with emphasis on E-ELBD features and mechanisms. Taxonomic and etiological frameworks driving the study's design will also be addressed in this chapter. Chapter 3 is an overview of the study's aims and study design. In brief summary, the primary aim (SA1) targeted cardinal features thought to be axiomatic for E-ELBD: paradoxical vocal fold adduction with inspiration and inspiratory dyspnea. For this aim, magnitude of glottal obstruction (SA1A) and perceived dyspnea severity (SA1B) were quantified at rest and during an attack-inducing exercise challenge in athletic adolescents diagnosed with E-ELBD, compared to findings for athletic control subjects. The goal of the secondary aim (SA2) was to identify auxiliary laryngeal patterns (i.e., supraglottic activity—arytenoid prolapse, epiglottic collapse, and ventricular compression) (SA2A) and symptoms (SA2B) from a comprehensive list of symptoms attributed to E-ELBD and investigate these findings within the same conditions as SA1. The exploratory aim (SA3) addressed two potential mechanisms involved in E-ELBD pathogenesis: altered autonomic (sympathovagal) balance (SA3A) (Ayres & Gabbott, 2002; Undem, McAlexander, & Hunter, 1999) and temperament (stress reactivity, a correlate to anxiety) (SA3B) (Al-Alwan & Kaminsky, 2012; Ferris, Eisele, & Tunkel, 1998; Husein et al., 2008; Kaufman, Mohebati, & Sotolongo, 2004; Lund, Garmel, Kaplan, & Tom, 1993; Nayar, Zanak, & Ahmed,

2003; Niggemann, 2010; R. Patterson, Schatz, & Horton, 1974; Powell et al., 2000; M. S. Smith, 1983; H. S. Snyder & Weiss, 1989). Chapters 4 and 5 are submission-ready chapters, divided into perceptual and physiological features of E-ELBD. Chapter 6 summarizes and synthesizes the dissertation study's findings and provides a description of potential future directions for this programmatic line of work.

2.0 BACKGROUND & THEORETICAL FRAMEWORKS

Correctly identifying individuals with E-ELBD is a challenge. No standard definition of E- ELBD exists and inclusion/exclusion criteria lack for observable clinical features (Christopher & Morris, 2010; Lima, 2012; and Campainha et al., 2012). Therefore, methods to correctly diagnose E-ELBD and thus prevent frequent mismanagement—the goal of this proposed study—are vital. Section 2.1 provides an overview and appraisal of traditional diagnostic approaches in ELBD as well as a summary regarding the importance of multidisciplinary study of ELBD to help improve diagnostic paradigms. Section 2.2 is a summary of the development of a comprehensive taxonomy framework for clinical features of ELBD, using previously proposed conceptual frameworks. Applications of the comprehensive taxonomy framework to the dissertation study's design will also be addressed in this section. A summary of potential underlying mechanisms driving clinical expressions of ELBD will be addressed in Section 2.3.

2.1 CURRENT ELBD DIAGNOSTIC STANDARDS

Standard diagnostic procedures for ELBD involve taking a clinical history to identify symptoms suggestive of ELBD; procedures may also involve a physical examination to rule out anatomical defects that could be causing symptoms as well as to identify abnormal laryngeal-respiratory patterns. Ancillary procedures such as pulmonary function testing (PFT) and measures of blood oxygenation levels may also be performed at the time of evaluation, depending on the medical

setting. Additional cardiopulmonary, exercise, psychological, allergy, or gastroesophageal testing may be warranted, depending on the ELBD presentation. Unfortunately, because no robust methods to diagnose ELBD exist, diagnostic protocols are largely based on patient report, symptom history, subjective clinical findings, and exclusion after other dyspneic-inducing conditions have been ruled out. Furthermore, symptom reporting can be a double-edged sword since symptoms are typically non-specific, have poor predictive value, and can mask the underlying problem as much as they can provide insights into causes.

2.1.1 Case history

Case history in the diagnosis of ELBD provides valuable information. Interview questions may pertain to signs and symptoms described by the patient, as well as predisposing or precipitating factors. Symptoms described by the patient can shed light on whether other disorders co-occur with or resemble ELBD (Martin et al., 1987). Clinicians may follow up with questions related to occurrence of dyspnea within the respiratory cycle, sensation of constriction in the throat or chest, presence of noisy breathing, onset, resolution, and duration of symptoms, and anything the patient has noticed that improves the symptoms or makes symptoms worse. Questions may relate to other physiological conditions including gastroesophageal or laryngopharygeal reflux disorders, voice problems, or presence of a chronic cough (Hoyte, 2013). Symptom-based questionnaires, such as the Dyspnea Index (DI) may be used to quantify perceived severity of dyspneic-related symptoms as they relate to quality of life (Gartner-Schmidt, Shembel, Zullo, & Rosen, 2014). Other questionnaires, such as the Cough Severity Index (CSI), Voice Handicap Index – 10 (VHI-10),

and the Reflux Severity Index (RSI) can all aid in the differential diagnosis of ELBD (Jacobson et al., 1997; Shembel, Rosen, Zullo, & Gartner-Schmidt, 2013).

2.1.2 Physical examination

The goal of the physical examination is to rule out upper airway obstruction of structural origin, laryngeal edema, and to appreciate acute signs of episodic ELBD (e.g., stridor, tachypnea, accessory muscle tightness, or clinical signs of heightened anxiety, panic or distress). Direct visualization of the larynx with flexible rhino-laryngoscopy (often referred to as flexible *laryngoscopy*) guided through the nose (transnasally) and pharyngeal cavity, with the tip of the camera lens near the laryngeal inlet (the opening that connects the pharynx and the larynx), is the current gold standard for diagnosing ELBD (Bahrainwala & Simon, 2001; Balkissoon & Kenn, 2012; Chiang et al., 2008; Christopher & Morris, 2010; Hoyte, 2013; Ibrahim et al., 2007). Once the laryngoscope is placed in the optimal position for visualizing laryngeal dynamics, the larynx is carefully observed in conjunction with inspiratory/expiratory cyclical respiratory patterns during a period of quiet metabolic breathing. The patient may also be asked to perform tasks such as sniffing, speaking, or sustaining vowels to rule out vocal fold paresis or paralysis as the cause of laryngeal obstruction and associated dyspnea.

During asymptomatic periods, when no respiratory distress is noted, the arytenoids and ventricular folds should be abducted, and the epiglottis should point upwards in such a way that the true vocal folds can be readily visualized on laryngoscopy (Blager, 2000). The true vocal folds should move slightly away from midline (abduct) during inspiration and should move slightly towards midline (adduct) on expiration (Brancatisano, Collett, & Engel, 1983; Klahn & Perlman,

1999; Yasushi Murakami & Kirchner, 1972). However, during symptomatic events, any number of laryngeal structures may move abnormally or paradoxically. The arytenoids can prolapse forwards and downwards, moving towards the open glottis, creating obstruction in the upper airways. The ventricular folds can compress medially or anteriorly-posteriorly. The true vocal folds can adduct on inspiration or expiration, reducing the area of the glottal lumen. Abnormal "twitching," "shaking," or "spasms" of the larynx have all been suggested to be characteristic of ELBD during both asymptomatic and symptomatic periods (Blager, 2000; Sandhu & Kuchai, 2013; Treole, Trudeau, & Forrest, 1999).

The majority of these purported abnormal laryngeal presentations require some sort of provocation challenge. The type of challenge is based on the triggers that induce the transient episodes in ELBD. For example, individuals with irritant-associated ELBD may be presented with perfume, ammonia, capsaicin, or methacholine. Stress may be induced in those with psychogenic-associated ELBD using a timed mental arithmetic test. Recent literature has also proposed the use of continuous laryngoscopy exercise (CLE) testing in individuals with exertion-associated ELBD using a treadmill, exercise trainer, or in the swimming pool[2] (Heimdal et al., 2006; Maat et al., 2009; Olivier, Argentão, Lima, da Silva, & dos Santos, 2013; Selner, Staudenmayer, Koepke, Harvey, & Christopher, 1987; Tervonen et al., 2009; Walsted et al., 2017). Ideally, trigger provocation should be conducted with simultaneous direct visualization of the larynx to be able to observe how the larynx responds to the instigating stimuli.

[2] Continuous laryngoscopy examinations with swimming have recently been described by Walsted et al., 2017 using an inner and outer swim cap, a laryngoscope, waterproof tape to secure the laryngoscope to the nose, and a battery powered hand-held monitor/recorder. See Walsted, E.S., Swanton, L.L., van Someren, K. et al. (2017). Laryngoscopy during swimming: A novel diagnostic technique to characterize swimming-induced laryngeal obstruction. *The Laryngoscope*. doi: 10.1002/larynx.26532, for details.

Various studies suggest laryngoscopy is a highly sensitive diagnostic method when individuals with ELBD are *symptomatic* (Sullivan, Heywood, & Beukelman, 2001). In a study by Newman and colleagues, abnormal laryngeal movement was accurately identified during acute dyspneic episodes in 100% of participants with known ELBD (Newman et al., 1995). However, although laryngoscopy is considered the current gold standard for diagnosing ELBD, according to a literature review by Christopher and Morris (2010), only 38% of patients are diagnosed with ELBD using direct endoscopic laryngeal visualization methods (Christopher & Morris, 2010).

Reasons for diagnosing ELBD without laryngoscopy are numerous. First, laryngoscopic equipment may not be available due to logistical or budget constraints. Second, because of the transient nature of ELBD, an episode may not always occur during the clinical examination or within the clinical setting. Third, medical professionals may not want to purposefully induce an episode out of concern the individual may not be able to pull out of the ELBD "attack." Fourth, laryngoscopy can be considered invasive. Even if an episode is induced during the clinical assessment, these events are understandably frightening, and the patient may not tolerate laryngoscopy during the event, resulting in a distressing situation for everyone involved (Bernstein, 2014; Hicks, Brugman, & Katial, 2008; Rhodes, 2008).

As a result of any number of these challenges, clinicians may resort to diagnosing patients with ELBD based on exclusion of symptoms, patient interview, or case history out of necessity. "Trial treatment" sessions, an inefficient and burdensome method from both the perspective of the patient, family/caregivers, and medical staff/resources, may also be used at times to confirm the diagnosis made by the referring physician (Bernstein, 2014; Gallena et al., 2013). Diagnostic therapy can be especially burdensome when symptoms do not improve with traditional therapy for ELBD and the symptoms mimicking ELBD are deemed representative of another condition

entirely. The realization that therapy is not helping typically occurs after 3-4 sessions once the "buy-in" and investment to partake in therapy with a speech-language pathologist has been made. Repercussions include frustration on the part of the patient or family and adverse effects on the credibility of the treating clinician and the field of speech-language pathology, in general.

When laryngoscopy *is* performed, incorporation of provocation challenge with laryngoscopy into standard clinical practice is the exception. Proponents of foregoing provocation challenge in conjunction with laryngoscopy believe there are distinct laryngeal presentations during asymptomatic periods that indicate ELBD. These presentations include laryngeal edema, erythema, and heightened oscillatory responses of the arytenoids to flexible endoscope in the laryngeal vestibule, causing a "twitchy"-like pattern of the corniculate cartilages and true vocal folds (Andrianopoulos, Gallivan, & Gallivan, 2000; Morrison & Rammage, 2010b; Rosen & Murry, 2000; Treole et al., 1999; A. E Vertigan, Gibson, Theodoros, & Winkworth, 2007). The thought is that because these characteristics, present at all times, are believed to indicate ELBD, the condition can be diagnosed without provocation. However, a dearth of comparisons of laryngeal presentations and responses amongst patients with ELBD, healthy normals, and other clinical populations lack. Therefore, whether these patterns are specific to the ELBD population and whether they are diagnostic indicators of ELBD is unknown.

The second rationale is that not everyone with suspected ELBD can be induced with provocation in the clinical setting. Since case history and symptom reporting are so heavily weighted in clinical decision making, a diagnosis of ELBD is provided and the patient treated accordingly, regardless of whether an event is provoked. The question then arises as to why provoke if the method does not necessarily change the plan of care. However, the absence of an ELBD attack may indicate some other condition mimicking ELBD symptoms and should be

considered when an ELBD attack cannot be elicited. Furthermore, when an event is provoked, the traditional method involves insertion of the laryngoscope *after* the instigating stimuli have been presented. Unfortunately, previously studies have shown that laryngeal responses to provocation can return to baseline very quickly after the instigating stimuli are withdrawn (Bernstein, 2014). That robust laryngeal responses to provocation are typically not detected with laryngeal examination after stimulus withdrawal is not surprising.

When laryngoscopy equipment is not available, other ancillary diagnostic procedures may be incorporated into the diagnostic assessment. The most common ancillary diagnostic procedure is pulmonary function testing (PFT) with flow-volume loops. During asymptomatic intervals, flow-volume loops appear normal in individuals with ELBD (and other variable extrathoracic obstruction), where the inspiratory loop takes on a U-shaped pattern (Figure 2-1A). During an episodic event, the inspiratory loop will be flat, truncated, and saw-toothed instead of U-shaped, while the expiratory loop continues to exhibit a normal shape (although at times the loop can appear to be diminished) (Figure 2-1B) (Balkissoon & Kenn, 2012; Mikita & Mikita, 2006; Tilles, 2003; Vlahakis, Patel, Maragos, & Beck, 2002). Inhaled methacholine challenge testing is typically used in individuals with lower airway pathology, but is also sometimes used in conjunction with PFT in individuals with ELBD. The protocol involves presentation of inhaled methacholine in increasing concentrations, with PFT performed prior to and after each incremental methacholine increase (Altman et al., 2002; Balkissoon, 2002; MacConnell & Danielsen, 2013; Murry et al., 2011; Newman & Dubester, 1994).

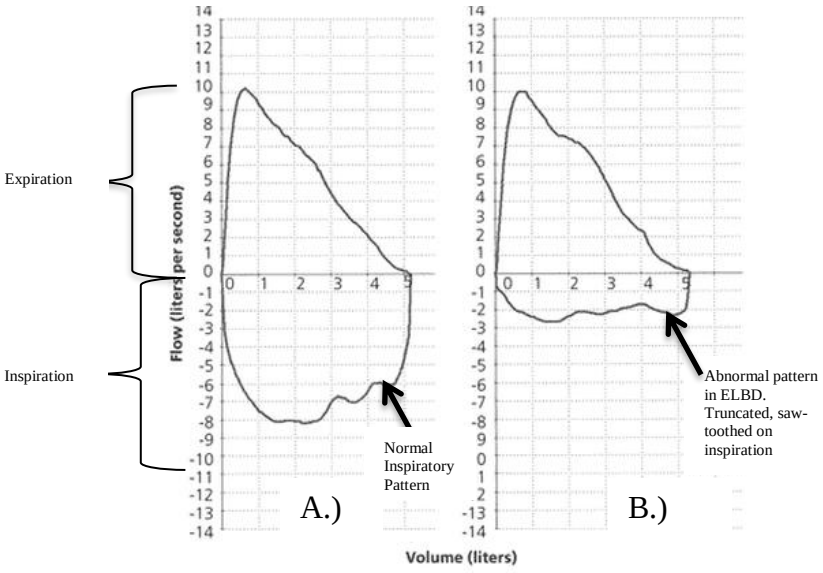


Figure 2-1. A.) Flow volume loops in normal healthy controls and B.) Flattened inspiratory loop with normal expiratory loop, consistent with ELBD. Flow (Liters/sec) is on the Y-Axis and volume (Liters) is on the X-Axis.

However, the diagnostic sensitivity and specificity of PFT and methacholine challenge in ELBD is uncertain. A review by Morris and colleagues (2006) showed only 28% of patients with ELBD exhibited inspiratory truncation on flow-volume loops when symptomatic. These same PFT patterns were also found in a cohort of individuals with ELBD during nasal provocation challenge (positive PFT results were found with 29% of symptomatic participants) (Olivier et al., 2013). However, in a study by Watson and colleagues (2009), flow-volume loops predicted severity of symptoms of ELBD, but results of PFTs were not predictive of simultaneous laryngoscopic findings. This is probably because laryngoscopic findings and perceived intensity of dyspneic symptoms (and as a result, PFTs) do not always directly correlate.

In a study to determine the sensitivity of methacholine challenge testing in patients with presumed ELBD, 34 participants (10 with ELBD, 12 with exercised-induced asthma, and 12 healthy controls) with normal flow-volume loops at baseline were recruited from a large army

medical center. Truncated inspiratory loops were found in four out of the ten (4/10) participants with presumed ELBD after exposure to methacholine, although two out of the four participants with positive inspiratory results showed inspiratory adduction of the vocal folds at baseline, despite the negative flow-volume loops found at that same time. One participant with exercise-induced asthma also had truncated flow-volume loops on inspiration, instead of the usual truncated and concave appearance on expiration indicative of asthma, after exposure to methacholine (Perkins & Morris, 2002). This result is suggestive of either a false positive result or undiagnosed extrathoracic airway pathology.

Results of these studies suggest flow-volume loops and methacholine challenge may not always be sensitive or specific to ELBD, but could be used to help differentiate ELBD from asthma based on differences in appearances of flow-volume loops between the two pathologies (see Figure 2-2 for details to distinguish between ELBD and asthma) (Guss & Mirza, 2006).

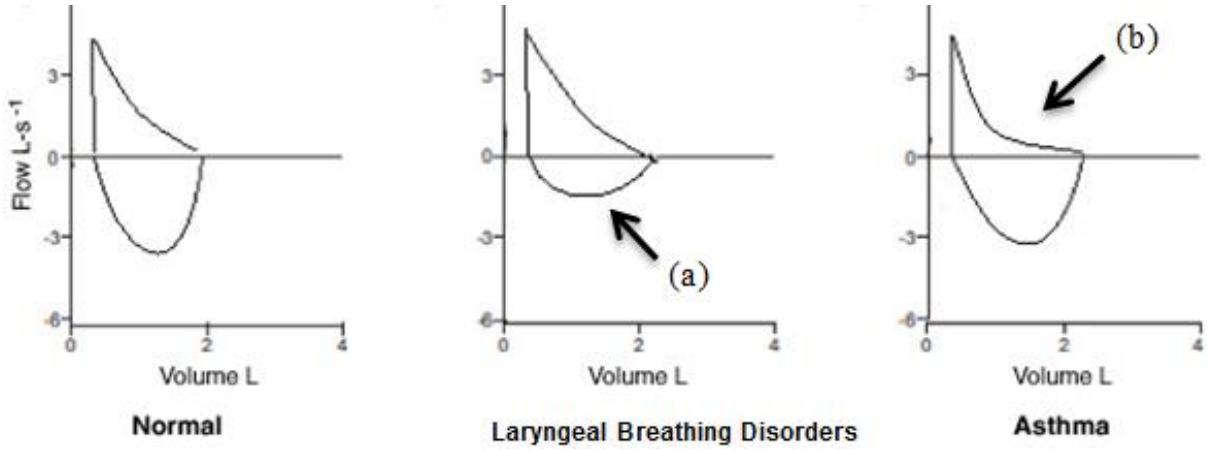


Figure 2-2. Flow volume loops during different respiratory pathologies. Flow (Liters/sec) is on the Y-Axis and volume (Liters) is on the X-Axis. The first flow volume loop is an example of normal breathing pattern. The second is an example of a flow volume loop during an ELBD episode. The third flow volume loop is an example of breathing patterns during an acute asthma attack. Letter (a) pointing to the middle flow volume loop shows truncation that can occur on inspiration with ELBD. The letter (b) pointing to the third loop demonstrates a "scooped" appearance on expiration that can occur with obstructive lung disease (e.g., asthma).

Methacholine challenge may also be more sensitive with certain types of ELBD (e.g., irritant-associated ELBD). If PFT and methacholine challenge testing is to be used, it should be performed in conjunction with laryngoscopy, but should not be used to influence the decision to perform laryngoscopy, and should not be performed in place of laryngoscopy, especially when structural laryngeal pathology has not been ruled out. This is especially true because flow volume loops may appear similar during the inspiratory phases in both fixed extrathoracic (laryngeal) obstruction (e.g., laryngeal stenosis; laryngeal neoplasms) (Figure 2-3(a)) and variable extrathoracic (laryngeal obstruction (e.g., ELBD) (Figure 2-3(b)), resulting in potential for misdiagnosis with serious consequences (e.g., failure to identify laryngeal cancer).

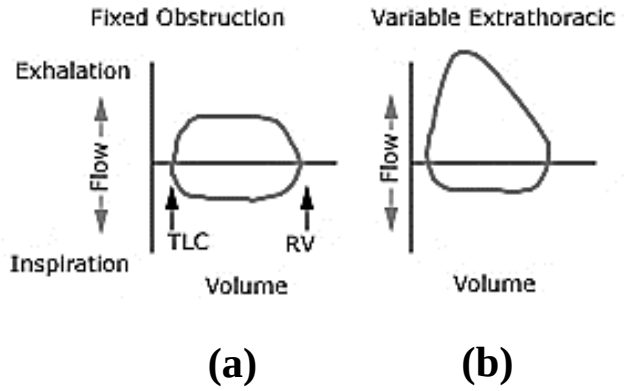


Figure 2-3. Flow volume loops for different types of airway pathologies. (a) Fixed extrathoracic obstruction (e.g., goiter, laryngeal stenosis, tracheal stenosis); (b) variable extrathoracic airway obstruction (e.g., tracheomalacia, vocal fold paralysis, ELBD). Inspiratory, but not expiratory, volumes are flat because of negative inspiratory pressures "sucking in" laryngeal or tracheal tissue. Conversely, expiratory flow is thought to blow the tissue "out of the way" during expiration. Or in the case of ELBD, paradoxical laryngeal movement patterns happen on inspiration but not expiration, due to unknown mechanisms involved in laryngeal patterns. Flow (Liters/sec) is on the Y-Axis and volume (Liters) is on the X-Axis.

2.1.3 Common concomitant disorders in differential diagnosis

A large part of the diagnostic differential process is to rule out other concomitant pathologies that could be either co-occurring with ELBD or mimicking ELBD symptoms. The conditions that most often co-occur with ELBD are chronic cough, non-organic dysphonic voice disorders (e.g., muscle tension dysphonia), gastro-esophageal and laryngo-pharyngeal reflux disorders, and pulmonary conditions. Inflammatory disorders, sino-nasal disorders, psychogenic disorders, and symptoms of dysphagia have also been suggested to commonly co-occur with ELBD, but their prevalence in, and relationship to, ELBD is largely unknown. These conditions are summarized in the following sections.

2.1.3.1 Chronic cough

Coughing is a normal physiological reflex, initiated by receptors within the larynx, to protect the sublaryngeal airways from foreign particulates. The reflex can be activated with any number of exogenous or endogenous stimuli, including, but not limited to, upper respiratory infections, smoking, lung pathology, reflux disorders, postnasal drip, and use of ACE inhibitors (Bolser & Davenport, 2002; Bolser et al., 2006; Boushey, Richardson, & Widdicombe, 1972; Cobeta, Pacheco, & Mora, 2013; Fontana & Lavorini, 2006; Irwin, Curley, & French, 1990; Rolla et al., 1998; Vertigan, Bone, & Gibson, 2013; Widdicombe, 1998).

When coughing becomes non-productive, refractory, and persists for more than 3 weeks without known underlying cause (e.g., upper respiratory infection), it is referred to as *chronic* cough (Chung, 2011; Milgrom et al., 1990). Although there may be no known physiological reason or benefit for the cough, chronic cough may be *precipitated* by a known event such as an upper

respiratory infection (URI), or may be present in individuals with asthma or chronic irritant exposure. Episodic symptoms of chronic cough usually start with a tickle or sensation in the larynx or pharynx, which quickly turn into coughing fits that can result in incontinence, lightheadedness, or syncopic events; these presentations can severely affect quality of life to the point of social isolation and agoraphobia (Dicpinigaitis, Lim, & Farmakidis, 2014; Hu et al., 2014; Minassian, Drutz, & Al-Badr, 2003; Puetz & Vakil, 1995). Symptoms may worsen with external (e.g., noxious fumes, temperature/weather change, exercise), internal (e.g., post-nasal drip, GERD/LPR), or psychological (e.g., stress, anxiety) triggers. The gold standard for the management of chronic cough is a combination of pharmacological intervention (e.g., reflux medication) and behavioral management (i.e., cough suppression therapy) (Gaziano & Serrano, 2012; Milgrom et al., 1990; Murry & Sapienza, 2010; Ryan, Vertigan, & Gibson, 2009).

2.1.3.2 Muscle tension dysphonia

Muscle tension dysphonia (MTD) is a voice disorder proposed to be characterized by normal laryngeal anatomy with so-called abnormal physiological coordination between respiratory and phonatory gestures (Gillespie et al., 2013; Hixon & Putnam, 1983; Rubin, Macdonald, & Blake, 2011). Signs and symptoms of MTD involve either the *sound* or the *feel* of voice production. Deviation in *sound* may include dysphonia, harsh vocal quality, or pitch breaks; deviation in the *feel* of the voice may include pain with phonation (odynophonia), vocal fatigue or effort, globus sensation, or shortness of breath (Koufman & Block, 1982; Sapienza, Al-Natour, Schmalz, & Ritter, 2000).

The exact "abnormal" laryngeal muscle patterns or underlying pathophysiological mechanisms that result in muscle tension have yet to be elucidated, although preliminary studies

suggest individuals with MTD have some combination of lower than normal lung volumes during phonation, increased extrinsic and supraglottic laryngeal muscle activity, greater laryngeal resistance and subglottal pressure, and increase in expiratory muscle activation (Gillespie et al., 2014; Gillespie et al., 2013; Hillman, 2004; Hillman et al., 1989; Mehta & Hillman, 2008).

2.1.3.3 Pulmonary disorders

A variety of obstructive and restrictive pulmonary conditions can co-occur with ELBD.[3] Reduction in airflow in obstructive disorders (e.g., asthma, COPD) occurs with increased secretions, inflammation, mucosal thickening, smooth muscle contraction (bronchoconstriction or bronchohyperresponsiveness), or edema due to chronic inflammation of the airways. Obstruction can also result from destruction of lung tissue (parenchyma). Obstructive diseases are characterized by a reduction in expiratory airflow (FEV_1 and FEV_1/FVC), which occurs when the diameter of the airways decreases or there is a loss of elasticity in the lungs. FEV_1 is the volume of air expired within the first second after full inspiration. In healthy normal individuals, FEV_1 is between 80-120% of average value, dependent on sex, age, and height. In individuals with obstructive disease, FEV_1 will be decreased because of increased airway resistance to expiratory airflow (West, 2012).

FVC is forced vital capacity, or the volume of air that can be fully blown out after full inspiration. In individuals with lung obstruction, FVC may be reduced due to the premature closure of the lower airway during expiration. FEV_1/FVC is the ratio between FEV_1 and FVC. Usually FEV_1 will be more reduced than FVC in obstructive disease. Tidal Volume (TV) is the amount of

[3] Of note, ELBD is considered a type of (variably) obstructive respiratory condition.

air inspired and expired during quiet breathing. In obstructed lungs, TV may be normal or increased if air is trapped in the lungs; if there is incomplete emptying of the lungs, over time the residual volume (RV) and overall volume of the lungs will increase (TLC). Bronchodilators to increase airway diameter or steroids to reduce inflammation within the airways are the standard of care for individuals with obstructive disease (West, 2012) (see Figure 2-4 for summary of physiological changes in obstructive disorders.

Physiological Changes in Obstructive Disorders					
Measure			Severity	FEV_1/FVC (% pred)	FEV_1 (% predicted)
FEV_1	Decreased		Normal	> 70	> 80
FEV_1/FVC	Decreased		Mild	< 70	> 80
FVC	Decreased or normal		Moderate	< 70	$50 \leq FEV_1 < 80$
TLC	Normal or increased		Severe	< 70	$30 \leq FEV_1 < 50$
RV	Normal or increased		Very severe	< 70	< 30 or < 50 with chronic respiratory failure

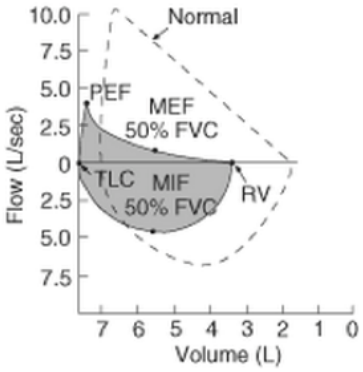


Figure 2-4. Volume and capacity changes in obstructive lung disease. Flow volume loop represents these changes in obstructive lung disease. Flow (Liters/sec) is on the Y-Axis and volume (Liters) is on the X-Axis. Acronyms: Peak expiratory flow (PEF); mid-expiratory flow (MEF); mid-inspiratory flow (MIF); forced vital capacity (FVC); total lung capacity (TLC); residual volume (RV).

The most common type of obstructive disorder that co-occurs with ELBD is asthma, with 30-40% of individuals with ELBD thought to have both asthma and ELBD (Christopher & Morris, 2010; Hicks et al., 2008; Hoyte, 2013). Asthma is a chronic inflammatory lower airway disease, characterized by noisy breathing on expiration (wheezing), tightness in the chest, shortness of breath, and cough. Asthma exacerbations, as with ELBD, begin with stimuli/triggers (e.g., allergens, smoking, pollution, viruses, and occupational exposure), resulting in acute episodes of

paroxysmal airway hyperresponsiveness and obstruction, commonly referred to as "asthma attacks" (Ates & Vaezi, 2014; Krouse et al., 2007).

To make matters more challenging, ELBD may also be *misdiagnosed* as asthma in 33-90% of cases due to the common overlap in symptom presentation between the two disorders (Koufman & Block, 2008; MacConnell & Danielsen, 20103.; Mikita & Mikita, 2006; Morris et al., 2006; Nascimento et al., 2013; Tilles & Inglis, 2009). Adverse effects resulting from misdiagnosis are not trivial. Data from a systematic review by Hoyte (2013) showed 90% of misdiagnosed patients with ELBD were erroneously given bronchodilators (52%) and systemic steroids (44%), the standard of care regimen for patients with asthma (Hoyte, 2013). Newman and Dubester (1994) found a high prevalence of individuals with ELBD (81%) on exceedingly high corticosteroid dosages for prolonged periods. Chronic and unnecessary corticosteroid use can result in iatrogenic Cushing's Syndrome (secondary to hypothalamic-pituitary axis suppression), obesity, osteoporosis, diabetes, and hypertension (Heinle, Linton, & Chidekel, 2003; Hicks et al., 2008; Mikita & Mikita, 2006; Newman et al., 1995).

Various methods to distinguish symptoms of asthma from symptoms of ELBD have been proposed to help reduce the occurrence of misdiagnosis. Unfortunately, the majority of the literature on the asthma/ELBD relationship, except one recent prospective, observational study by Bernstein (2014), is based on expert opinion. A summary of reported clinical features and their differences between ELBD and asthma from the vantage point of expert opinion (Christopher & Morris, 2010; Gallena et al., 2013; Hoyte, 2013; Nascimento et al., 2013; Ritz, Steptoe et al., 2006; Sarafino & Goldfedder, 1995; Tilles & Inglis, 2009) and from the perspective of patient-reporting (Bernstein, 2014) is shown in Table 2-1. Inconsistencies are most prominent between expert opinion versus patient-report with regard to timing of noisy breathing within the respiratory cycle,

recurrent symptom rates with additional trigger presentation, and duration of recovery time without treatment.

Specifically, conventional wisdom based on expert opinion considers noisy breathing to happen on inspiration (stridor) in individuals with ELBD and on expiration (wheeze) in individuals with asthma. However, according to patient self-report, both stridor and wheezing can occur equally during episodes of ELBD and acute asthma episodes, suggesting timing of noisy breathing as a criterion in the differential should be considered with caution. Additionally, symptoms in ELBD are thought to return after repeated exposure of trigger stimuli, usually with increased severity during the second exposure. However, patient-reported symptoms suggest this occurs in less than half of individuals with ELBD. Last, symptoms in ELBD are believed to resolve as quickly as they occurred, but the study by Bernstein (2014) showed more than half of individuals with ELBD were still symptomatic more than an hour after the episode was triggered. According to the results of the study by Bernstein (2014), the following clinical features may help distinguish asthma from ELBD: the disorder may point towards asthma if the individual responds positively to bronchodilators, and if there is presence of chest tightness and (possibly) wheezing. Symptoms may point towards ELBD if the individual has no response to bronchodilators, and if throat tightness is present (Bernstein, 2014).

Table 2-1. Upper Versus Lower Respiratory Tract Pathology: Steps Towards Differential Diagnosis.[4]

Clinical Presentation	Signs & Symptoms (Expert Opinions)		Signs & Symptom (Patient-reported)	
	ELBD	Asthma	ELBD	Asthma
Occurrence Timing	Immediate onset (within 5 minutes)	Gradual onset	69% immediate	62% immediate
Tightness	In throat	Middle or lower chest	90% in throat 65% in chest	48% in throat 100% in chest
Difficulty Breathing	On inhalation	With exhalation	Not addressed	Not addressed
Noisy breathing	Stridor	Wheezing	50% Stridor 40% Wheeze	52% Stridor 76% Wheeze
Recurrence	Symptoms can occur immediately and more severely when trigger resumes	Symptoms tend to be less severe when trigger removed or bronchodilators are used	40% re-occurrence worse with re-initiation of trigger	52% re-occurrence worse with re-initiation of trigger
Recovery Time (without treatment)	May take less than 10 minutes	Usually takes up to an hour without medication	65% of symptoms lasted longer than an hour without treatment	84% symptoms lasted longer than an hour without treatment
Medications	Bronchodilators won't help	Bronchodilators will help	6% resolution with bronchodilators	79% full resolution with bronchodilators
Triggers	Irritant (internal, external), physical activity, psychological factors	Allergens, pollution, physical activity, psychological factors, aspirin, hormonal	Exercise: 52% Irritant (external): 55% Irritant (internal – reflux): 55%	Exercise: 65% Irritant (external): 88% Irritant (internal – reflux): 28%

[4] Expert opinion columns based on work by Christopher & Morris, 2010; Gallena et al., 2013; Hoyte, 2013; Nascimento et al., 2013; Ritz, Steptoe et al., 2006; Sarafino & Goldfedder, 1995; Tilles & Inglis, 2009. Patient reported columns are based on a prospective study by Bernstein (2014).

2.1.3.4 Rhinosinusitis and reflux disorders

Systemic irritation conditions are commonly associated with ELBD, especially in the irritant-associated ELBD variant. Gastroesophageal Reflux Disorder (GERD)[5] and laryngopharyngeal reflux disorder (LPR) have been reported to co-occur in up 95% of individuals with ELBD (Loughlin & Koufman, 1996; Powell et al., 2000). GERD results from relaxation of the lower esophageal sphincter, while LPR involves relaxation of the upper esophageal sphincter. Primary symptoms of GERD are heartburn and indigestion; primary symptoms of LPR are increased mucus production, sour taste, cough, or globus sensation. In a study by Cukier-Blaj et and colleagues (2008), 71% of patients with ELBD exhibited abnormal laryngopharyngeal sensitivity thresholds and reported abnormally high scores on the Reflux Severity Index (RSI), a patient-centered questionnaire targeting severity of reflux symptoms. Individuals with ELBD may also have concomitant postnasal drip (PND), allergic rhinitis, or vasomotor rhinitis. These nasal disorders include symptoms of sneezing, nasal discharge and obstruction, and rhinorrhea. Concomitant cough, bronchoconstriction, and hyper-secretion of mucus in the airways may also be present (Annesi-Maesano, 2003; Rajakulasingam & Durham, 2003).

2.1.4 Multidisciplinary Nature of ELBD Differential Diagnosis

The differential diagnosis of ELBD requires multidisciplinary collaboration. Distinctions between ELBD and structural abnormalities necessitate direct visualization of the larynx with laryngoscopy or bronchoscopy, which require a laryngology or pulmonology evaluation. A differential diagnosis

[5] GERD can occur in ELBD either by gastric juices entering the laryngeal vestibule directly due to a relaxed lower esophageal sphincter (characteristic of GERD). Literature has also suggested GERD may also occur with ELBD with distal stimulation of laryngeal vagal afferents (Heatley & Swift, 1996).

between ELBD and allergic, inflammatory, or autoimmune processes (or the influence of one on the other) may involve an ear, nose, and throat (ENT) physician or allergy specialist. Differentiating between ELBD and pulmonary conditions usually warrants a pulmonary evaluation, and may even include an additional consult with a respiratory therapist, depending on whether lower respiratory tract pathology is suspected. Symptoms of many psychogenic disorders overlap with symptoms of ELBD; as a result, individuals with ELBD may find themselves sitting on the proverbial psychotherapist's couch. To complicate matters further, a psychological assessment may actually be warranted if ELBD are influenced by psychogenic factors. If the ELBD are associated with exertion, the individuals with ELBD may also be referred for consults in the field of cardiopulmonary or sports medicine. ELBD that are triggered by endogenous irritants such as post-nasal drip or reflux disorders may require the expertise of an ENT physician or a gastroenterologist, depending on the source of irritation. When individuals with ELBD finally receive their correct diagnosis, they usually are referred to a speech-language pathologist for treatment (Appelblatt & Baker, 1981; Gimenez & Zafra, 2011; Mathers-Schmidt, 2001; Vasudev, 2012). The speech-language pathologist typically continues to collaborate with other medical professionals when concurrent pharmacological management is provided.

To add an additional layer of complication, all of these disciplines must be informed about the various clinical features and presentations involved in ELBD in order to appropriately manage this spectrum of conditions. Each specialty must not only know how to treat the underlying factors that may be related to etiology or may cause episodic triggers, but must also be able to understand the relationship of these factors in the presentation and etiology of ELBD, in and of themselves. These challenges highlight the fundamental need for multidisciplinary collaboration and a network of professionals with interdisciplinary knowledge to best manage ELBD.

2.2 CLINICAL FEATURE FRAMEWORKS IN ELBD

Descriptions of ELBD in the medical literature go back as far as 1842, when Robley Dunglison first described symptoms in his book, *The Practice of Medicine*, as "hysteric croup" consisting of "a long-protracted, loud and convulsive cough, followed, at times, by the crowing inspiration, and by dyspnea so great as to threaten suffocation." The role of the larynx in these presentations was noted by Sir Morell Mackenzie, who directly visualized the larynx with a laryngeal mirror and found "intermittent abnormal movement within the larynx" (Mackenzie, 1869). Since Dunglison's and Mackenzie's descriptions of ELBD over 140 years ago, over 200 clinical observations of ELBD have been documented in various bodies of literature (Maat et al., 2011) across a multitude of medical domains (see Table 2-2 for examples).

Table 2-2. Multiple Disciplinary Contributions to the Study of Laryngeal Breathing Disorders

Disciplines that study and manage episodic laryngeal breathing disorders (ELBD)			
Allergy	Gastroenterology	Otolaryngology	Pulmonary
Alternative Medicine	General Surgery	Otorhinology	Respiratory Therapy
Anesthesiology	Immunology	Pediatrics	Speech-Language Pathology
Computational Biology	Neurology	Pharmacy	Sports Medicine
Emergency Medicine	Nursing	Primary Care	Sports Psychology
Endocrinology	Nutrition	Psychiatry/ Psychology	Thoracic

Therefore, it is surprising that knowledge in this area has not evolved much beyond descriptive observations and expert opinion. The shortage of systematic studies on ELBD, combined with "siloed" knowledge according to medical domain, has made it nearly impossible

to identify clinical patterns and generalize findings across the ELBD spectrum. These gaps have left medical providers to diagnose ELBD based on differential exclusion and to make clinical decisions based on unsubstantiated claims. These substandard diagnostic approaches explain why individuals with ELBD are so frequently misdiagnosed (up to 90%) and why it takes so long for their condition to be correctly identified (average 7.5 years) (Bernstein, 2014; Newman, Mason, & Schmaling, 1995; Traister, Fajt, Whitman-Purves, Anderson, & Petrov, 2013; Koufman & Block, 2008; MacConnell & Danielsen, 20103.; Mikita & Mikita, 2006; Morris et al., 2006; Nascimento et al., 2013; Tilles & Inglis, 2009). The lack of diagnostic standards also brings into question appropriate inclusionary criteria for future studies that test hypotheses about underlying mechanisms and raises doubt on the validity of the few studies that have been conducted on ELBD in the past.

To summarize, the extensive variation in clinical features across the ELBD spectrum, the involvement of multiple disciplinary concepts with little multidisciplinary cross-talk, and the lack of robust empirical evidence preclude a comprehensive appreciation of ELBD topography across the spectrum. The establishment of comprehensive concepts and methods of study would seem beneficial from both an academic and clinical perspective. From an academic perspective, the establishment of a comprehensive picture of ELBD will allow investigators to accurately identify appropriate cohorts of participants for research recruitment purposes. Such an establishment will also provide structure when identifying consensus and discrepancy within the literature needing further study. From a clinical perspective, these approaches would allow clinicians to recognize affected individuals with ELBD more readily, thereby reducing chances of misdiagnosis and mismanagement of patients with ELBD.

Theoretical frameworks can be used to identify various phenotypic—or the observable characteristics of a condition—variants from multiple disciplinary vantage points. Theoretical frameworks can also be used in the academic study of ELBD. Conceptual models are appropriate when no universal standards or guidelines exist in that they provide a schema and necessary groundwork from which to begin to understand or study a phenomenon. In the context of ELBD, conceptual models can be used to identify working (prototypic) definitions and inclusion criteria for ELBD; they can also provide a systematic method for identifying subgroups and studying phenotypic topography within the various clinical presentations. However, the downside to conceptual models is that they are based on assumption, and should therefore be treated as dynamic working paradigms that change and evolve with new empirical knowledge.

Several conceptual models have been proposed within the ELBD literature. Unfortunately, these models are narrow in their concepts and either fail to address or exclude one or more ELBD feature variants, creating challenging for appreciation of the Gestalt of ELBD and the accurate study of its topography. Therefore, a more comprehensive conceptual framework was necessary to unify and synthesize various clinical feature observations and presentations (i.e., phenotypes). The first goal in this endeavor was to review and appraise, as well as to compare and contrast, available conceptual frameworks in the literature that addressed clinical presentations of ELBD. These three conceptual models have been summarized in Section 2.2.1. An analytic look at how to incorporate these models into a broader conceptual framework for clinical feature taxonomy has been provided in Section 2.2.2. Integrated concepts amongst these conceptual frameworks became part of a larger, comprehensive taxonomic framework of clinical features across the ELBD spectrum, described in Section 2.2.3.

2.2.1 Previous Conceptual Frameworks in the ELBD Literature

2.2.1.1 Irritable larynx syndrome model

Irritable Larynx Syndrome (ILS) is a conceptual model based on the etiological assumption the larynx becomes hyper-responsive with over-exposure to exogenous or endogenous irritants, causing long-lasting "neuroplastic" changes in the brain, and resulting in laryngeal muscle "misuse" (Morrison, Rammage, & Emami, 1999). Individuals with ILS experience *episodic laryngospasms* in which the "glottis closes down in such a way as to inhibit airflow" (Morrison et al., 1999). When these episodes occur, "patients complain of variants of laryngospasm[6] or dysphonia, or both, and their symptoms are triggered by something definitive" (Morrison et al., 1999). Individuals with ILS also exhibit symptoms of chronic cough, globus sensation, or throat clearing. Palpable evidence of accessory and strap muscle tension, as well as anterior-posterior contraction of the larynx (observed on laryngoscopy) may be present (Morrison et al., 1999). The noted symptoms lead to muscle "misuse" resulting in vocal cord dysfunction, muscle tension dysphonia, and chronic cough (Morrison et al., 1999).

Any number of irritant-based triggers may precipitate these symptoms, including strong fragrances, noxious fumes, cleaning supplies, foods, odors, airborne particles, voice use, coughing, tobacco smoke, post nasal drip, reflux, cold air, and sudden temperature changes (Jaradeh et al.,

[6] Although the term "laryngospasm" connotes a physiological presentation, Morrison and colleagues use the term to mean both a *physical presentation* (i.e., observable spasms of the larynx and resultant reflexive laryngeal obstruction on laryngoscopy), as well as a *symptom* ("patients *complain* of laryngospasms"). The discrepant terminology can lead to nomenclature and definition confusion. For the purposes of this review, the term *dyspnea* will be used to connote *symptoms* of laryngospasm, while the term *laryngospasm* will be reserved for laryngoscopic findings to minimize confusion. Interchanging *dyspnea* with *laryngospasm* in this situation is permissible because a.) Morrison and colleagues allude to the symptom multiple times in both their 1999 and 2010 publications, and b.) the standard definition of laryngospasm directly links laryngeal spasm (confirmed by laryngoscopy) to consequent impeding respiration (Alalami, Ayoub, & Baraka, 2008; Fink, 1956; Roy & Lerman, 1988).

2000; MacConnell et al., 2014; Morrison et al., 1999; Perkner et al., 1998; Powell et al., 2000). ILS is excluded when organic or "neurological" laryngeal pathology is present, or an identifiable psychiatric diagnosis can be made (Morrison et al., 1999). However, the authors acknowledge "emotions" may play a phenotypic or endotypic (underlying mechanisms driving clinical expression) role.

These same investigators conducted a study involving 39 patients who had a working diagnosis of ILS. Results showed dyspnea and dysphonia were the two major symptoms of ILS, with secondary symptoms including globus, cough, and perilaryngeal pain. The most common triggers reported were airborne irritants and gastroesophageal reflux disease (GERD). Viral illnesses as precipitating factors were reported in half of the patients (e.g., flu, herpes, viral meningitis, Lyme disease), and GERD was a concomitant disorder in almost all individuals (Morrison et al., 1999).

However, in a later publication, the authors reconsidered their position on cough as being a secondary symptom of ILS, and proposed it be considered a primary symptom, along with symptoms of dyspnea and dysphonia (Morrison & Rammage, 2010a). Addendums also included a bigger role of psychogenic factors in the ILS model, with reference to the authors' patients who often presented to the clinic with accompanying symptoms of anxiety or depression, "especially with sudden and distressing episodes of laryngospasm or cough" (Morrison & Rammage, 2010a). Additional contributions in the latter publication involved (1) more specific details on supraglottic paradoxical patterns: anteroposterior and lateromedial compression, where the former involves the "draw[ing] together" of the epiglottis and arytenoids, and the latter involves "squeezing of either the glottis or supraglottic structures" and (2) improvement of the definition of laryngospasm: "term used to denote airway obstruction, more often inspiratory than expiratory, characterized by

adduction of the true vocal folds. Recurring or bothersome laryngospasm was also called ‘vocal cord dysfunction’ (VCD) or ‘paradoxical vocal fold motion disorder’ (PVFMD)” (Morrison & Rammage, 2010a).

Conceptually, the ILS model may represent clinical presentations specific to certain phenotypic variants of ELBD, including irritant sensitivity and symptoms involving dyspneic, dysphonic, and cough patterns. Perkner and colleagues, as well as Andrianopolus and colleagues reported similar symptoms in patients with ELBD who had apparent irritant-based triggers. In the study by Perkner et al., (1998) irritant-associated ELBD was appreciated in 11 individuals within 24 hours after exposure to smoke, dust, fumes, gas, and vapors. Common symptoms included dyspnea (100%), cough (100%), noisy breathing (70%), choking/throat tightness (90%), chest pain/tightness (100%), and voice changes (100%) (Perkner et al., 1998).

In a retrospective study by Andrianopoulos and colleagues, irritant-variant ELBD was appreciated in 10 out of 27 participants with, what the authors referred to as *episodic paroxysmal laryngospasm* (EPL). Medical chart review included demographic information, diagnostic procedures used, medical management, comorbidities, and signs and symptoms. This medical information was included for any patient with documented “upper airway obstruction,” paradoxical vocal cord motion (PVCM), or paradoxical vocal cord dysfunction (PVCD). Triggers in this cohort included various foods, perfumes, air pollutants, and chemical agents. Common symptoms were acute respiratory distress (60%), dyspnea (44%), cough (60%), noisy breathing (70%), choking/throat tightness (60%), chest pain/tightness (16%), and voice changes (20%). Results of this study must be interpreted with caution for two reasons. First, symptom complaints of individuals with and without sensitivity to irritants were reported together, even after the authors acknowledged phenotypic differences. Second, the distinction between respiratory distress and

dyspnea was not clear. Regardless, somewhat alarmingly, complaints of respiratory distress and dyspnea[7] only occurred in about half of individuals included in the study, suggesting the cohort chosen for this study may not have been the appropriate target (Andrianopoulos et al., 2000; Perkner et al., 1998). Third, it was unclear what kinds of laryngeal responses were considered "paradoxical" for the study's inclusionary criteria.

The ILS model as a conceptual model may be beneficial for investigations specific to individuals with irritant sensitivity. However, this model excludes other trigger variants, such as those relating to exertion, and is based on the unsubstantiated assumption that symptoms directly related to respiration (i.e., dyspnea) and their corollaries (i.e., cough, dysphonia) are all due to the same underlying mechanism (muscle *misuse*). Until direct causal relationships can be made,[8] inclusion of behaviors not *directly* related to respiration and laryngeal *breathing* pathology should be treated with caution. Additionally, the model does not distinguish primary/direct *causal* symptoms of ELBD from resultant symptoms of other pathology related to ELBD. For instance, dyspnea is a primary symptom of ELBD caused by laryngeal obstruction. Conversely, the inability to "catch one's breath" is secondary to, or a result of, a coughing episode. (see Figure 2-5 for schematic representation).

[7] Hallmark symptoms of laryngospasms, PVCM, and PVCD (all terms used to connote laryngeal *breathing* disorders)
[8] Identifying muscle *misuse* on laryngeal electromyography (L-EMG), for example.

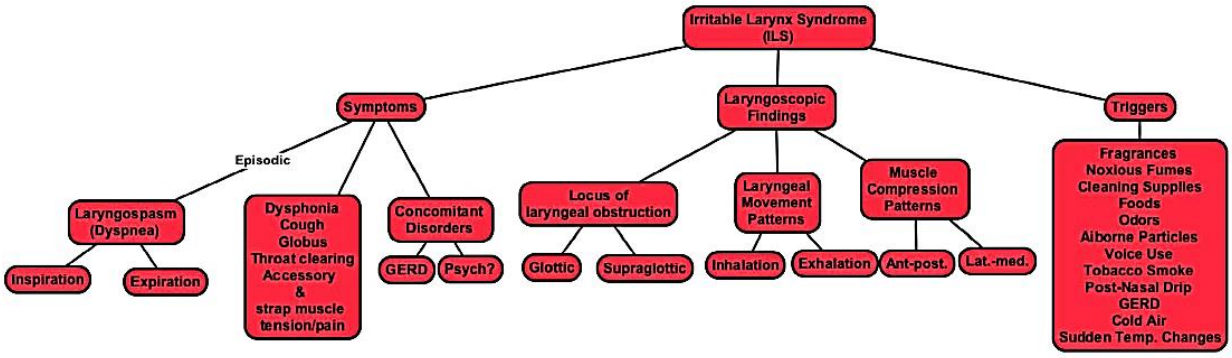


Figure 2-5. Irritable Larynx Syndrome schematic. Model divided into three subgroups: symptoms, laryngeal findings, and triggers.

2.2.1.2 Dichotomous model

The dichotomous model categorizes ELBD into one of two trigger-induced groups: *exercise-induced vocal cord dysfunction* (EIVCD) and *spontaneous vocal cord dysfunction* (SVCD). The predominant symptom in EIVCD and SVCD is shortness of breath during inspiration, which may also include symptoms of noisy breathing (stridor). The model was developed based on a retrospective chart review of 49 pediatric patients (Doshi & Weinberger, 2006). In this review, patient demographics, concomitant diagnoses, treatment recommendations, criteria for the diagnosis of laryngeal obstruction, procedures performed, and post-treatment outcomes were gathered from patients' charts. Based on history of recurrent symptoms, two phenotypic classifications were identified from this retrospective chart review: 20 in the spontaneous phenotypic group and 29 in the exercise phenotypic group. Once the categories had been identified, a decision was made to prescribe anticholinergic inhalers to the exercise-induced phenotypic group and "speech therapy" to individuals with the spontaneous phenotype (Doshi & Weinberger, 2006).

As far as general concepts go, the dichotomous model may be appropriate for individuals who experience dyspnea on exertion. Unfortunately, this model is flawed on multiple levels, from both a conceptual and an analytical perspective. Conceptually, as with the ILS model, the dichotomous model excludes other trigger stimuli variants. Because no further effort to identify phenotypic variables within the spontaneous vocal cord dysfunction group was made, it is unclear whether alternative clusters of phenotypic variants were present within this group. Additionally, the model was constructed using a pediatric cohort and must be interpreted with caution when applying it to the general ELBD population. Last, there was no mention of additional triggers in the exercise group that could contribute to episodes of ELBD. Analytically, data analysis methods, experimental protocol methods, and treatment protocols were not described, which can be problematic for future model appraisal, additional analysis, and replication of the study.

The second concern relates to diagnostic inclusionary criteria. The study cohort was determined based on (1) direct laryngoscopy, (2) reversible inspiratory airflow obstruction with spirometry in symptomatic patients, or (3) "convincing history of episodic inspiratory stridor" (Doshi & Weinberger, 2006). However, only 59% of participants were diagnosed with laryngoscopy, and over a third received a diagnosis based solely on patient interview. As a result, it is difficult to conclude all participants in this cohort had symptoms of dyspnea *caused* by laryngeal obstruction.

For participants who did undergo laryngoscopy, there were no descriptions of laryngeal findings in the ELBD cohorts. Other previous studies using direct laryngoscopy suggest laryngeal presentation may differ with exercise-associated ELBD as compared to other variants. In a study by Christensen and colleagues, paradoxical glottal movement of the true vocal folds, as well as supraglottic prolapse of the arytenoids, were noted during a continuous laryngoscopy exercise

(CLE) test in the majority of 97 adolescent athletes diagnosed with ELBD (Christensen et al., 2010). Abu-Hasan and colleagues (2005) also found paradoxical glottal movement, as well as arytenoid and epiglottal prolapse, but the latter presentation only occurred in 13 out of the 142 participants with exercise-induced dyspnea during a similar exercise task. Conceptually, these laryngoscopic findings, coupled with identifiable triggers, may provide valuable information for identification of phenotypic variants or subgroups relating to athletes with ELBD. Analytically, variation in laryngoscopic findings can improve the sensitivity of phenotypic frameworks in general (see Figure 2-6 for schematic representation of the Dichotomous Triggers model).

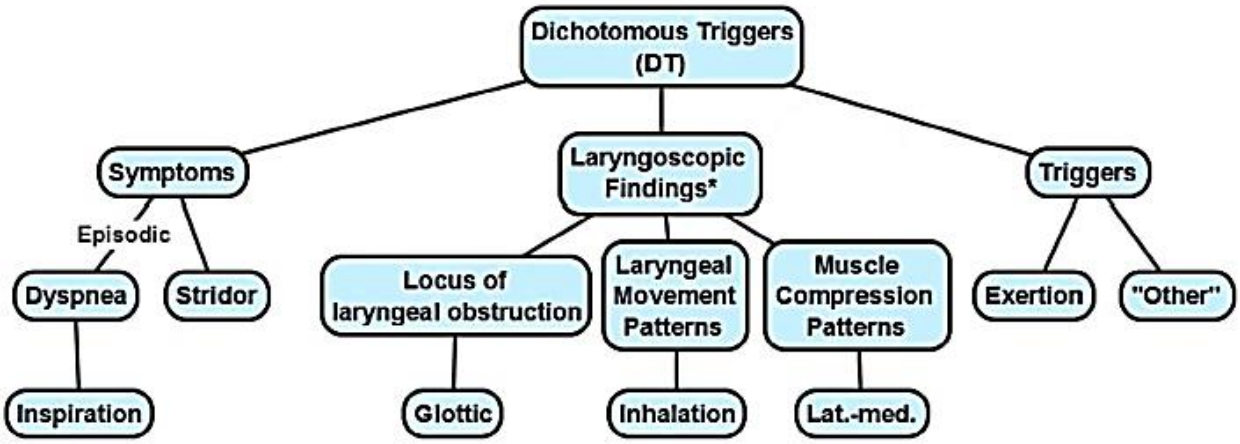


Figure 2-6. Dichotomous Triggers model. The model identified three issues: Symptoms, laryngeal findings, and triggers. Typical "paradoxical" laryngoscopic findings were described in the Introduction section of the paper on Dichotomous Triggers, and were therefore included in the model's schematic. However, no descriptions of laryngeal patterns specific to the two ELBD cohorts were described in the study.

2.2.1.3 Periodic occurrence of laryngeal obstruction (POLO) model

The primary symptom in the Periodic Occurrence of Laryngeal Obstruction (POLO) conceptual model is dyspnea with exposure to triggers. Noisy breathing (stridor), chest/throat tightness may be associated with dyspneic symptoms (Christopher & Morris, 2010). Complaint of cough and

voice changes (dysphonia) in the POLO model is not uncommon. However, in direct contrast to the ILS model, Christopher and Morris propose treating symptoms of cough and dysphonia as discrete, concomitant entities, binning or "splitting" various laryngeal-based symptoms until further empirical study can elucidate their etiological relationships and phenotypic roles in the definition and inclusion of ELBD (Christopher & Morris, 2010). Positive laryngoscopic findings are corollary to symptoms of dyspnea in the model. Identified structural pathology on laryngoscopy (e.g., laryngomalacia), pathologies of known etiology (e.g., laryngospasm secondary to intubation), and obstructive airway lesions (e.g., Reinke's edema) are considered exclusionary for the condition.

The POLO model divides laryngoscopic findings into two categories based on locus of obstruction: glottic and supraglottic. Supraglottic obstruction usually occurs on inspiration, whereas glottic obstruction may occur during both inspiration and expiration. Locus of laryngeal obstruction is then further divided into three categories, based on trigger stimuli: irritants, exertion, or psychogenic. POLO classification based on locus of laryngeal obstruction will first be addressed; a description of classification based on trigger variants will follow (see Figure 2-7 for schematic representation of the POLO model).

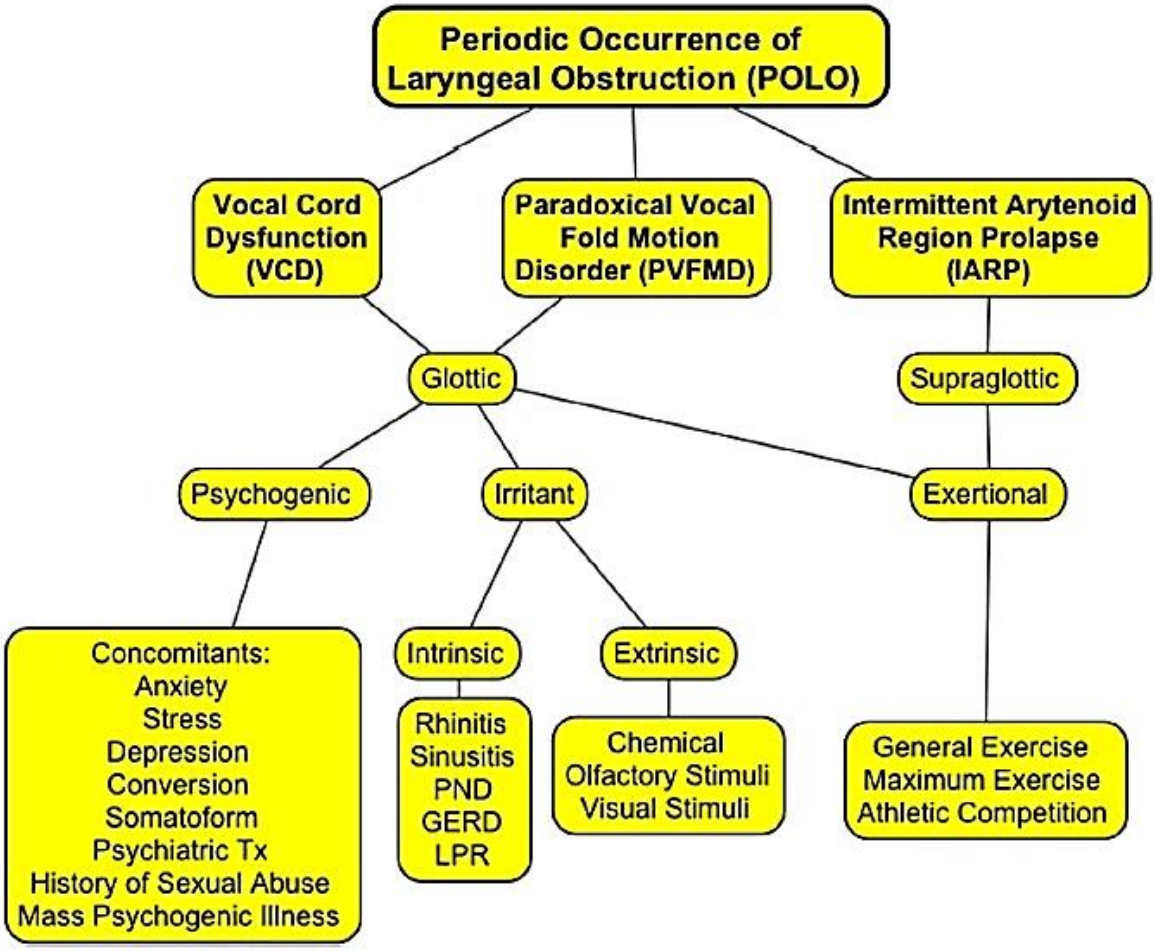


Figure 2-7. Schematic representation of the POLO model. Three types of ELBD are identified: Vocal cord dysfunction, paradoxical vocal fold motion disorder, and intermittent arytenoid prolapse (adapted from Christopher and Morris, 2010).

2.2.1.3.1 Locus of laryngeal obstruction

In the POLO model, laryngeal obstruction at the supraglottic level is referred to as *inter-arytenoid region prolapse*, or IARP.[9] Paradoxical supraglottic movement includes anterior or medial motion

[9] Special care should be taken not to confuse *laryngomalacia* or *arytenoid subluxation* with IARP. Laryngomalacia is a structural abnormality involving the cartilaginous structure of the larynx that is too pliable. It is usually seen in the pediatric population. The latter involves disruption of the cricoarytenoid joint. It predominantly occurs with severe blunt force laryngeal trauma. Both require surgery to mitigate the obstructed airway.

of the arytenoids or arytenoid tissue during respiration, resulting in a prolapse of the arytenoids over the glottic region. Prolapsed arytenoids are thought to occur with substantial negative inspiratory pressures (i.e., Bernoulli effect, Venturi effect) or alteration in muscle tone, causing laryngeal tissues to draw together (Bent et al., 1996; Christopher & Morris, 2010). These significant pressure changes may occur during maximum exertion or strenuous physical activity, which may explain why supraglottic obstruction is thought to be prevalent in athletes (Christopher & Morris, 2010; Atsushi Nagai, Kanemura, & Konno, 1992; Pinho, Tsuji, Sennes, & Menezes, 1997); however, prevalence of these findings has not been empirically studied in this cohort of individuals with ELBD. The stridor that sometimes accompanies IARP has been speculated to come from vibration of the corniculate cartilages (Christopher & Morris, 2010), although this hypothesis has also not been tested. Paradoxical movement of the true vocal folds may also accompany IARP, but yet again, this claim has not been tested and the rate of co-occurrence of glottal and supraglottic patterns are unknown. Although the arytenoids are mentioned as a locus of potential supraglottic obstruction, there is no other mention of supraglottic structures that may also cause obstruction, such as the epiglottis, aryepiglottic folds, or ventricular (false) vocal folds.

Glottic obstruction in the POLO model is referred to as *paradoxical vocal fold motion disorder* (PVFMD) and *vocal cord dysfunction* (VCD). In both PVFMD and VCD, the true vocal folds abnormally adduct towards midline on inspiration. Lateromedial compression on inspiration (only) is classified as PVFMD; lateromedial compression with inspiration and expiration is classified as VCD according to the POLO model (Christopher & Morris, 2010).

2.2.1.3.2 Trigger categories and conditions

The POLO model is similar to the ILS and dichotomous models in that it identifies various stimuli that induce dyspneic episodes. The first category, irritant-induced POLO, is similar in concept to

the ILS model. As the name suggests, irritants are responsible for laryngeal obstruction and episodic dyspnea. Irritants in the POLO model can be further classified into "extrinsic" (from the environment) or "intrinsic" (from within the body) triggers. Extrinsic irritants are anything found in the environment that is noxious to olfaction, including (but not limited to) chemicals, fumes, perfumes, or cleaning supplies. The authors also mention "visual stimulants" as triggers, but what is meant by "visual" is unclear. Intrinsic irritants can either stem from supralaryngeal (e.g., postnasal drip) or sublaryngeal (e.g., LPR/GERD) sources (Christopher & Morris, 2010).

The second category, exertion-induced POLO, parallels the dichotomous model. Exertional triggers include exercise, athletic competition, or even activities of daily living (ADL), especially in deconditioned individuals. Because this trigger variant is prevalent in athletes, the symptoms are often mistaken for exercise-induced asthma (EIA) (Christopher & Morris, 2010).

The third category, psychogenic-induced POLO, is the least well defined of the three trigger categories. It is unclear whether psychosomatic factors actually *trigger* episodic ELBD or whether these factors are *concomitant* in individuals with ELBD. Nevertheless, psychogenic influences in the POLO model include (1) anxiety, (2) stress, (3) depression, (4) "somatoform disorder"[10], (5) "conversion disorder," (6) psychiatric history, (7) history of sexual abuse, and (8) "mass psychogenic illness" (Christopher & Morris, 2010).

Conceptually, the POLO model is the most comprehensive of the three conceptual models, in that it considers other phenotypic presentations besides triggers, and makes attempts to compare laryngeal findings with respective triggers. As a result, a more comprehensive presentation of ELBD across multiple possible variants can be appreciated. However, because the prevalence of

[10] "Somatoform disorder" was renamed in the DSM-5. Both "somatoform disorder" and "conversion disorder" are subcategories of somatic symptom disorder.

laryngeal findings with certain trigger variants has not yet been directly (prospectively) studied, placing triggers within the category of locus of obstruction may, at this time, be premature. The same can be said for classification of symptoms related to laryngeal behaviors. Symptoms of cough and dysphonia are treated as divergent entities within the POLO framework. The authors make a proposal to "split" these symptoms until otherwise noted, but do not provide rationale for their decision.

Section 2.2.2 provides an analytic look at approaches to the classification of ELBD clinical features. These methods were used to inform the composition of the comprehensive taxonomy framework, described in Section 2.2.3.

2.2.2 An analytical look at ELBD classification

In their literature review on ELBD, Christopher and Morris (2010) discuss two approaches to categorizing ELBD concepts related to laryngeal behaviors: *lumping* and *splitting.* The lumping approach classifies and defines any clinical features in ELBD as primary symptoms based on the hypothesis they share clinical features and have the same anatomical or pathophysiological origin. The ILS model is a classic example of the lumping method. Laryngeal behaviors, including dyspnea, dysphonia, and cough, in the ILS model are assumed in the same inclusionary definition because they all come from the glottis (origin) and involve muscle "misuse" (pathophysiology). Although Christopher and Morris suggest treating symptoms of cough and dysphonia as separate entities, they do recommend the lumping approach for certain situations so as to not get "bog[ged] down with the process of classification and speculation regarding specific cause[s]." Laryngeal variations in locus of laryngeal obstruction, glottal patterns, and its triggers can be considered a form of lumping into the conceptual framework of the POLO model (Christopher & Morris, 2010).

The authors then suggest the predetermined classification system can be used to evolve concepts with better appreciation of what is "in the [classification] box" (Christopher & Morris, 2010).

Conversely, the *splitting* approach classifies laryngeal behaviors (e.g., airway protection, communication, respiratory modulation) into separate categories in the POLO model. Within the framework of ELBD, laryngeal behaviors that beget dyspnea are considered inclusionary, while behaviors related to coughing or communication fall into distinct categories. Splitting focuses on the study of differences in clinical features and their underlying mechanisms in relation to dyspneic-inducing laryngeal behaviors. Christopher and Morris advocate first lumping laryngeal characteristics related to dyspnea into the same inclusionary definition of ELBD and then appraising the differences among their associated signs and symptoms (i.e., locus of obstruction, trigger types that induce obstruction) (Christopher & Morris, 2010).

The splitting approach may be a preferable method for building a framework for ELBD. Conceptually, splitting laryngeal behaviors (e.g., airway protection, communication, respiratory modulation) may be sensible when underlying pathophysiological mechanisms are largely unknown and normal physiological mechanisms are not well understood. Otherwise the framework may be erroneously built on false pretense if the underlying assumption is incorrect. Analytically, studying mechanisms separately for each laryngeal behavior and its associated pathological symptom(s) provides a systematic approach to understanding physiological and pathophysiological mechanisms and their relationships in laryngeal behavior. In other words, studying laryngeal behaviors separately and then considering their overlap once mechanisms are better understood yields less error as compared to starting with an assumption and delineating mechanistic differences from said assumption.

Figure 2-8 is a visual representation of a proposed analytical framework to systematically evaluate mechanisms involved in laryngeal behaviors and resultant pathological symptoms. The schematic is by no means comprehensive; the goal is to illustrate the benefit of using the splitting analysis method. The splitting approach starts with (1) normal physiological mechanisms involved in laryngeal behaviors (respiratory modulation, airway protection, and communication), the (2) influences of structural or anatomical origin (at the supralaryngeal, laryngeal, and sublaryngeal levels), (3) examples of pathological causal mechanisms (white boxes), and (4) resultant pathophysiological symptoms (dyspnea, cough, dysphonia).

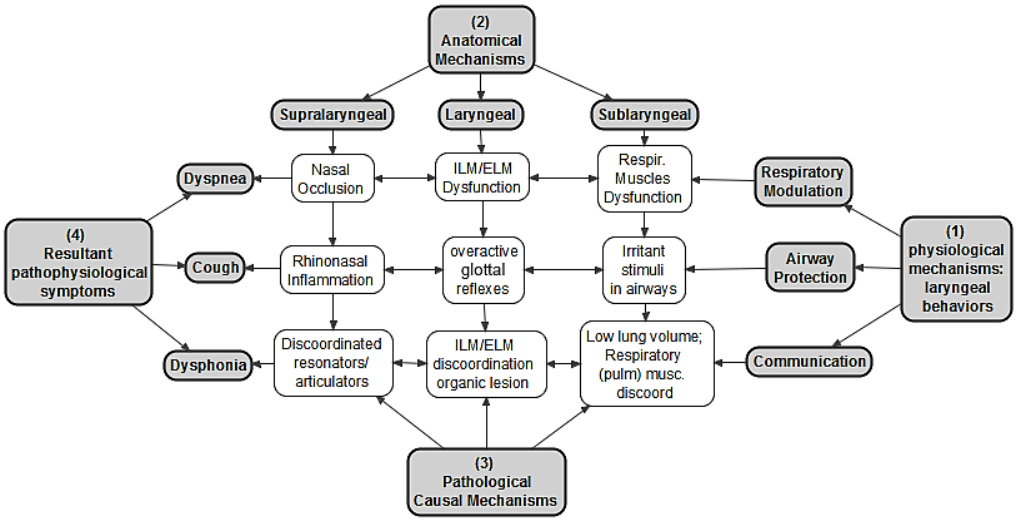


Figure 2-8. Physiological and pathophysiological mechanisms involved in various laryngeal behaviors including ELBD and other voice and laryngeal-associated symptoms.

2.2.3 Comprehensive Taxonomy Framework

Previously proposed conceptual frameworks in ELBD presentation may be myopic when used in isolation, but when considered together, provide a nice blueprint for comprehensive taxonomy frameworks in the study of ELBD. Integrating the three previously proposed conceptual models

in the ELBD literature increases reliability of reported clinical features in ELBD across various disciplines, and reduces the potential for "unknown unknowns." Conceptually, integration of the three models provides a more comprehensive platform than consideration of any of the models alone for working definitions, inclusion criteria, and identification of subgroup clusters that may otherwise have been missed without a systematic approach. Analytically, the integrated models can be used to systematically appraise current literature, can identify areas of discrepancy and gaps requiring further investigation, and can provide a springboard for future interdisciplinary discussion and consensus.

Consensus across the models provided a springboard for a working definition of ELBD, as well as identification of applicable inclusion criteria and potential subgroups for the dissertation study. Inconsistencies and discrepancies in concepts across the conceptual models provided an analytical platform for an additional literature review and future study investigations. The second literature review (Section 2.2.3.2) culminated in an updated comprehensive framework (Section 2.2.3.3) and drove the dissertation study's research design (Chapter 3).

2.2.3.1 Original Comprehensive Taxonomy Framework

Figure 2-9 is a schematic representation of an original comprehensive taxonomy framework, based on integration of the three previously proposed conceptual models: Irritable Larynx Syndrome (ILS), Dichotomous Triggers (DT), and Periodic Occurrence of Laryngeal Obstruction (POLO). This framework was lumped into three categories: (1) characteristics of laryngeal-respiratory kinematics ("Laryngoscopic Findings" in Figure 2-9), self-reported symptoms ("Symptoms" in Figure 2-9), and episode-inducing triggers ("Triggers" in Figure 2-9). Integrated concepts found across all three models are represented in grey boxes (solid borders). The grey boxes show that all three previously proposed models (ILS, DT, and POLO) reported episodic periods of inspiratory

dyspnea as the primary symptom in ELBD. All three models also agree that this primary dyspneic symptom is a direct result of laryngeal obstruction at the glottal level, with abnormal lateromedial adduction occurring within the inspiratory respiratory cycle. Last, the three models recognize stimuli of various kinds trigger these acute clinical presentations of dyspneic symptoms and correlative laryngeal findings. Conceptual overlap in the models can be constructed into the following operational definition of ELBD: *trigger-induced glottic obstruction presenting as episodic inspiratory dyspnea*. This operational definition was used to inform the dissertation study's experimental design.

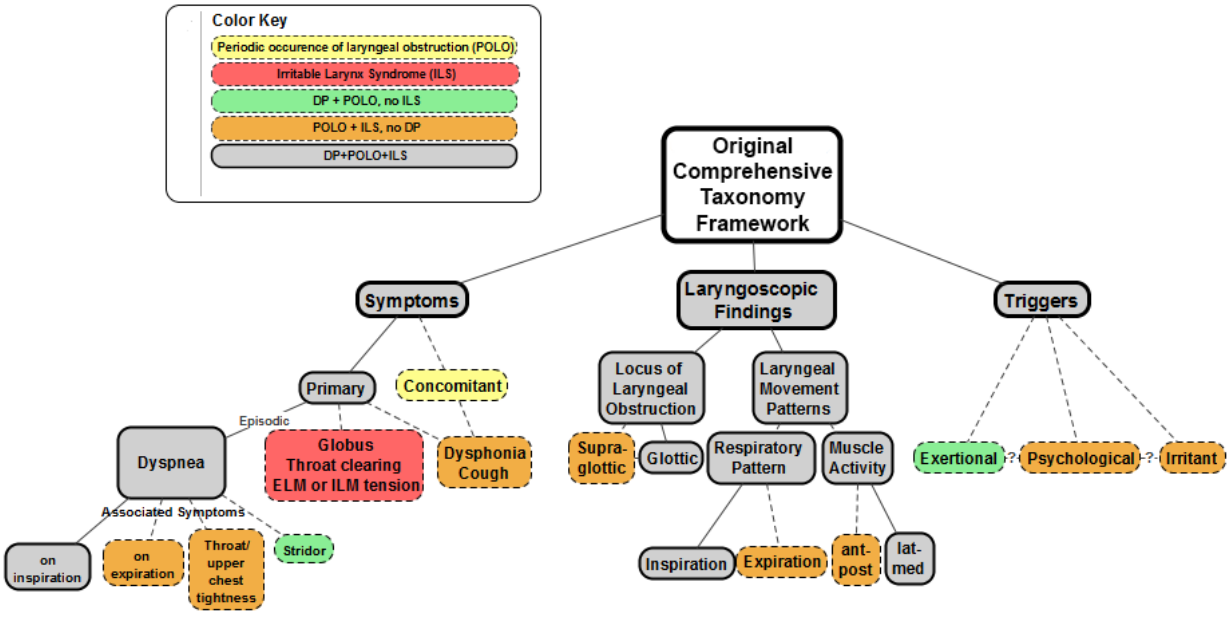


Figure 2-9. Original comprehensive taxonomy framework. The framework is based on the following three models: Irritable Larynx Syndrome (ILS), Dichotomous Triggers (DT), and Periodic Occurrence of Laryngeal Obstruction (POLO). Grey (solid) boxes represent clinical features common across the three ELBD models (ILS, DT, and POLO). Colored (dotted) boxes represent feature discrepancies across the models. ELM = extrinsic laryngeal muscle. ILM = intrinsic laryngeal muscle. Ant-post. = anterior-posterior. Lat-med. = lateral-medial.

Colored boxes (dotted borders) in Figure 2-9 represent inconsistency and discrepancy across the three conceptual models. These boxes provide a systematic visual method to identify areas requiring further investigation. In some situations, clinical features were not addressed across all the models, including symptoms of dyspnea on expiratory phase, upper body tightness, or stridor. The presence of supraglottic obstruction, expiratory patterns within the respiratory cycle, and anteroposterior laryngeal muscle patterns were also not universal across all models. Last, the variety in reported triggers across the model suggest there are different stimuli that cause these acute presentations of clinical signs and symptoms.

A few hypotheses may provide explanation for these findings. First, it could be that the clinical features variably described are not common across all types of ELBD within the condition spectrum. The second reason could have to do with "unknown unknowns." Some clinical features may not have been reported simply because they were not considered. As the authors of the POLO models mention, "if you don't think about it, you can't diagnose it" (Christopher & Morris, 2010). A third reason for inconsistencies or discrepancies across the models could be due to clinical feature over-reporting where some of the mentioned features may not be indicative of ELBD, but may instead represent other co-occurring conditions. For example, psychogenic disorders, addressed in the POLO model, may co-occur with ELBD but may not actually be a trigger that induces episodes. Expiratory vocal fold adduction may be a normal variant in commonly co-occurring pulmonary disorders, but are not indicative of ELBD pathophysiology. Symptoms of cough or dysphonia in the ILS and POLO models may co-occur with ELBD, and may signify a separate but concomitant disorder. Referring back to Figure 2-9, the colored boxes also show discrepancy in interpretation of clinical features across the three models. Specifically, the POLO model treats symptoms of cough and dysphonia as concomitant, yet distinct entities, while in the

ILS model, these symptoms are considered primary symptoms of ELBD. Further study involving physiological and pathophysiological mechanisms relating to the larynx in various laryngeal behaviors, combined with patient-centered symptom reporting, is needed to elucidate the role of laryngeal behaviors in the ELBD framework.

The next sections will focus on the current literature in ELBD presentation using the three *lumped* categories of clinical feature classification as a guide: laryngeal-respiratory dynamics, self-reported symptoms, and episodic triggers. The ways in which these categories can be used to study the role of various *split* features in ELBD presentation and pathophysiology will also be addressed.

2.2.3.2 Additional Literature Review for Updated Comprehensive Taxonomy Framework

2.2.3.2.1 Laryngeal-respiratory dynamics

The majority of research on laryngeal-respiratory kinematics can be found in the voice, speech, and swallowing literature. However, because breathing patterns for these tasks have kinematic properties distinct from those for vegetative breathing at rest and with different ventilatory demands (e.g., exercise) (Moore, Caulfield, & Green, 2001), extrapolating findings from these other areas of work to the ELBD population can be problematic. There is a common misconception that glottal configuration remains constant in respiratory dynamics within healthy populations (Scheinherr et al., 2015). Furthermore, the majority of work in laryngeal function for breathing has been conducted in quadrupedal, anesthetized, and tracheotomized animal models. The downside to generalizing findings directly from these animal models, without taking into account differences between subject types and study protocol methods, can result in misunderstanding of laryngeal-respiratory dynamics in awake, behaving humans. First, respiratory biomechanics in quadrupedal animals likely differ from those of bipedal animals (i.e., humans), due to variations in gravitational

pull of respiratory muscles (caudal versus ventral positioning). Gravitational differences could mean different muscle combinations are involved in laryngeal-pulmonary coupling. Second, pharmacological agents used in anesthesia, such as ketamine and xylazine, have been shown to affect respiratory patterns (Erhardt, Hebestedt, Aschenbrenner, Pichotka, & Blümel, 1984). Therefore, whether (and how) these breathing patterns differ in eupneic humans versus anesthetized animals is largely unknown. How airflow affects laryngeal configuration and laryngeal-pulmonary muscle coordination has yet to be compared in tracheotomized and non-tracheotomized subjects.

Having said as much, what *is* known of laryngeal dynamics during tidal breathing in *humans* is that laryngeal breathing involves stereotypic, phasic, synchronized movement patterns controlled by respiratory musculature (Nagai et al. 2005). The larynx acts as a respiratory conduit during these cyclical laryngeal-pulmonary dynamics, working to modulate airflow and airway resistance. During quiet, vegetative inspiration, the vocal fold abduct. The increase in glottal aperture is thought to facilitate greater airflow and oxygen intake (Brancatisano, Collett, et al., 1983; Brancatisano, Dodd, & Engel, 1983). These patterns primarily involve the cricothyroid (CT) and posterior cricoarytenoids (PCA) laryngeal muscles (Helou, 2014; Hillel, 2001; Hlastala & Berger, 2001).

Right before the start of the expiratory phase for tidal breathing, the vocal folds begin to move passively towards midline and the glottis continues to narrow through 95% of the expiratory cycle (Brancatisano et al., 1983; Collett, Brancatisano, & Engel, 1983). This pattern is thought to occur as a direct result of CT and PCA deactivation (Helou, 2014; Hillel, 2001; Hlastala & Berger, 2001) and is believed to play a role in optimizing ventilatory gas exchange required to maintain metabolic homeostasis (Hlastala & Berger, 2001). Literature has shown the glottis typically

narrows between 10-14% throughout most of the expiratory phase in healthy normals during quiet breathing (Brancatisano et al., 1983; Collett, Brancatisano, & Engel, 1983).

However, the vocal folds can adduct by as much as 40% during expiration, depending on the individual's ventilatory needs. For example, these expiratory patterns occur when the pulmonary system needs more time to exchange oxygen with carbon dioxide in the presence of lung irritants, resistive load, or lung obstruction (England & Bartlett, 1982; Hoyte, 2013; Ibrahim et al., 2007; Jain et al., 2006; Kenn & Balkissoon, 2011; Murakami & Kirchner, 1972). This phenomenon, commonly seen in individuals with asthma and other obstructive conditions, is known as *positive end-expiratory pressure*, or *auto-PEEP*. In addition to auto-PEEP maximizing the duration of exposure of the respiratory membrane to gases within the alveoli, the laryngeal response is also thought to, in turn, reduce respiratory muscle load, prevent hyperventilation, and decrease chronic lung inflation that can occur over time (Jamilla, Stevens, & Szidon, 2000). These findings suggest increased expiratory vocal fold narrowing, in certain contexts, is a normal response (Collett, Brancatisano, & Engel, 1986; England, Ho, & Zamel, 1985; Hicks et al., 2008; Higenbottam, 1980; Hoyte, 2013; Jamilla et al., 2000; Kenn & Balkissoon, 2011; Martin et al., 1987; O'Donnell, Sanii, Anthonisen, & Younes, 1987; Patterson & O'Connell, 1994). The take-home point may that in the case of ELBD, adductory patterns during expiration should not be deemed pathological in certain situations, such as in the 30-40% of individuals with ELBD with concomitant asthma or with respiratory muscle fatigue or discoordination (Christopher & Morris, 2010; Hicks et al., 2008; Hoyte, 2013).

Below the level of the larynx, muscles within the lung-thoracic unit during quiet, non-phonatory breathing appear to correlate, at least partially, with laryngeal movement. Slight activation of the diaphragm and external intercostals occurs immediately after the onset of glottal

opening, and becomes passive during expiration, allowing elastic forces within the lung-thoracic unit to recoil to resting expiratory level before another respiratory cycle is initiated (Zemlin, 1998). The delicate interplay between the larynx and pulmonary system during inspiration increases negative pressures within the thoracic cavity, causing atmospheric air to enter the lungs. Increasing glottic aperture during inspiration also decreases airway resistance, thereby decreasing respiratory system effort and optimizing ventilation.

With exposure to strong irritants or other chemo- or mechano-*sensory* stimuli, the larynx takes on the role of airway *gatekeeper*, abruptly and reflexively adducting the vocal folds to protect the lower airways and lungs (Butani & O'Connell, 1997; Hoyte, 2013; Kenn & Balkissoon, 2011; Sasaki & Weaver, 1997). These patterns play a key role in tasks such as cough, swallowing, and diving and can occur during inspiration or expiration, depending on when the instigating stimulus occurs (Arteaga-Solis et al., 2013; Dempsey & Pack, 1995; Mukhopadhyay, Bates, Manney, & Ayres, 2007). Laryngeal adductor response to sensory stimuli is a physiologically normal means to protect the lower airways. These adductory patterns are also thought to compensate for ventilatory needs by increasing resistive load and modulating duration of volume-time courses of lung volumes to maximize ventilatory gas exchange. Unfortunately, these physiological patterns are often erroneously deemed "paradoxical" in the ELBD population. This is especially the case in patients with "laryngospasms" where complete glottal spastic adductory responses occur with sensory stimuli.

In addition to CT and PCA activation, the thyroarytenoid (TA), intrarytenoids (IA), and lateral cricoarytenoids (LCA) are thought to play a role in airway protection during inspiration. During expiration, the same list of intrinsic laryngeal muscles, in addition to the oblique transverse arytenoids and aryepiglottic folds, all activate to protect the lower airways from foreign

particulates. Within the pulmonary system, the diaphragm, external intercostals, scalenes, sternocleidomastoid, upper trapezius, levator costorum, paraspinals, and subclavius are active during the inspiratory phase. During expiration, the transversus thoracic, internal intercostals, rectus abdominus, transverse abdominus, external and internal obliques, pectoralis, serratus anterior posterior, and latissimus dorsi activate (Hlastala & Berger, 2001) to protect the lower airways as well by contracting in synchrony to expel foreign substance from the airways and into the oral cavity.

Alternately, with exposure to *mechanical* stimuli—such as with strenuous physical activity—the larynx takes on the role of respiratory *modulator*. Instead of adducting the vocal folds to protect the lower airways (i.e., gatekeeping in response to instigating sensory stimuli), the vocal folds during exercise abduct even more with inspiration (compared to resting state) to accommodate increased ventilatory demands (Brancatisano, Collett, et al., 1983). During expiration, the vocal folds are also thought to abduct with, on average, 74% increases in glottal configuration, as compared to rest, resulting in a 67% decrease in laryngeal resistance (Hurbis, Schild, & others, 1991; Maat, 2011; Maat et al., 2011). However, previous studies have also shown expiratory laryngeal responses can decrease (adduct) with high ventilatory demands. These patterns may be compensatory to prevent speed of thoracic collapse and reduce extrathoracic muscle load during exercise (Collett et al., 1986, 1983).

Part of the variability in findings for expiration may have to do with methodological inconsistencies across studies. In only a handful of cases were laryngeal patterns directly visualized during provocation challenges (e.g., irritants, exercise). In the few instances where laryngeal responses were evaluated in conjunction with stimuli, the larynx was visualized after the provocation was presented, making it unclear whether laryngeal response patterns were a direct

result of provocation (Echternach, Verse, Delb, & Richter, 2009; Matthias Echternach, Delb, Verse, & Richter, 2008; El-Kersh, Gauhar, Cavallazzi, & Perez, 2014; Fowler, Gore, Vyas, & Haines, 2010; Murry, Cukier-Blaj, Kelleher, & Malki, 2011).

The clinical culture of describing "pathology" without direct comparisons to normal physiological response to stimuli in the field of clinical voice disorders has left what is considered "abnormal" open to interpretation. For example, in a study by Treole and colleagues (1999), the term laryngeal "shakes" was used to describe atypical laryngeal kinematics in a cohort with supposed ELBD (Treole et al., 1999). However, in another study by Brancatisano and colleagues (1983), this same pattern was observed during laryngoscopy in healthy normal individuals and was attributed to a normal response to a foreign object (i.e., laryngoscope) near the laryngeal vestibule (Brancatisano et al., 1983). Tervonen and colleagues (2009) found "physiological slight and fast adduction of the vocal cords during expiration" in 13 of 15 control participants with no laryngeal dyspneic pathology, soon after laryngoscopy was initiated, in the absence of other provocation. While some consider a "twitchy" or "shaky" larynx a sign of pathology (Corey, Gungor, & Karnell, 1998), other investigators consider these patterns no more pathological than a reactionary eye blink (Brancatisano, Collett, et al., 1983; England & Bartlett, 1982; Tervonen et al., 2009; Wood & Milgrom, 1996). The benchmark for pathology could depend on the *threshold* or *amount* of laryngeal response, not by the pattern or presence of the response.

In addition to the variability in glottal configuration patterns, supraglottic patterns and their interpretations have also been shown to vary across studies. In general, during normal at rest tidal breathing, the epiglottis, arytenoids, and ventricular folds remain stationary in their abducted position. Intrinsic muscles of the larynx during physical activity help stabilize these supralaryngeal structures. The stylopharyneus, palatopharyngeaeus, and hyglossus muscles also work with the

laryngeal muscles to maintain laryngeal inlet dilation, forward epiglottic tilt, and aryepiglottic fold lengthening (Belmont & Grundfast, 1984; Maat, 2011; Maat et al., 2011). Inefficient innervation to any of these muscles can contribute to reduced laryngeal tension resulting in inspiratory inward suction of the laryngeal structures. Paradoxical supraglottic patterns can involve anterior or medial motion or the arytenoids or arytenoid tissue, resulting in a prolapse of the arytenoids over the glottic region. Arytenoid prolapse is thought to be more prevalent in the adolescent athlete population, and a 0-3 severity scale (see details in Section 3.2.2.2), previously validated in individuals with exercise-induced ELBD, has been used to identify severity of pathological supraglottic features (Maat, 2011). However, whether this supraglottic pattern is indicative of ELBD is unknown due to the lack of normative comparisons and therefore warrants prospective study. Another example of laryngeal pattern discrepancy has to do with the presence of a posterior glottal gap, or "chink," thought to be pathognomonic of ELBD. This hallmark clinical feature was first referenced in a case series by Christopher and colleagues (1983), and has since been cited in various bodies of literature (Chiang et al., 2008; Gallivan, 2001; Morris & Christopher, 2010; Nacci et al., 2010; Sullivan et al., 2001). However, in a literature review spanning 36 years of publications relating to ELBD, Brugman (2003) found account of posterior glottal gap in only 5-6% of cases.

Overall, the discrepancies across the literature on laryngeal-respiratory dynamics have to do with (1) the probable variance in presentations across the ELBD spectrum, (2) poor appreciation for *normal* physiological laryngeal movement, (3) lack of standardized methods for defining normal from *abnormal*, and (4) general scarcity in well-controlled studies. These gaps have resulted in unsubstantiated, qualitatively-based assumptions and reliance on idiosyncratic descriptors in diagnosis. Such methodological and conceptual gaps are concerning considering

qualitative descriptors of laryngoscopic findings are the current "gold standard" in diagnosing ELBD. Therefore, better defined models are needed of normal and disordered breathing at rest and with sensory and mechanical stimuli delivered to the laryngeal-respiratory system. As stated by Getty, "If we are to know physiologic and pathologic changes, we must know the normal" (Getty, 1975).

One method to address concerns surrounding the lack of robust methods to delineate pathology is through the use of quantitative approaches to laryngeal pattern responses. A recent study by Shembel and colleagues (2015) validated the use of anterior glottal angle measurements to study non-phonatory laryngeal configurations in an animal model (Shembel, Kolouri, Xu, & Abbott, 2015). In this study, measures of digital still images of 24 excised canine cadaver larynges were compared to measures of each corresponding physical canine larynx. The effects of (1) glottic aperture, (2) fiber-optic barrel distortion, and (3) camera lens perspective on the accuracy of laryngeal morphometry estimates were also evaluated. Results showed anterior glottal angle measurements for the quantification of non-phonatory laryngeal patterns to be reliable across raters. Results also showed accuracy on the same parameter between physical larynges and corresponding digital images (see Figure 2-10 for visual representation of anterior glottal angle method). Of note, anterior glottal angle was used as one of the primary outcome variables for the dissertation study. The method was further validated as a viable quantification method for studying laryngeal responses at rest and with exercise challenge in participants with and without ELBD. The method and its application to the dissertation study is further described in Section 3.1.1.

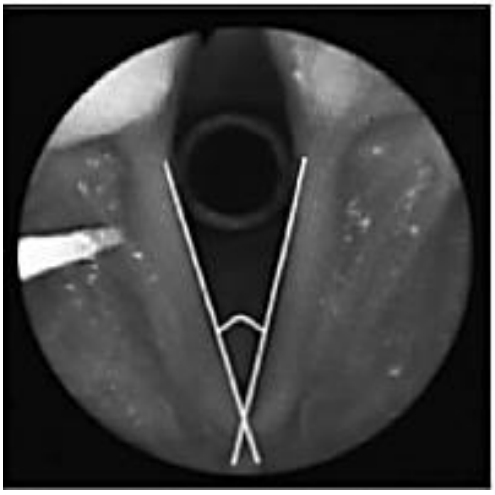


Figure 2-10. Anterior glottal angle measurements (Shembel et al., 2015).

2.2.3.2.2 Self-reported symptoms

Dyspnea is considered to be the hallmark symptom in patients with ELBD (Shembel et al., 2017). However, this sensation is not specific to ELBD; anyone with respiratory or pulmonary pathology can experience dyspnea. In fact, dyspnea may not even indicate pathology. Who among us has not experienced shortness of breath while running up a steep hill? If everyone gets short of breath when they exercise, what makes "normal" dyspnea different from "abnormal" dyspnea? To complicate matters further, the types of dyspnea perceptions can vary (e.g., breathing "difficulty" does not equate to breathing "discomfort") and can be influenced by social and cultural norms, previous experiences, and the individual's lexicon (Banzett et al., 2015; Crisafulli & Clini, 2010).

Descriptions of dyspnea include shortness of breath, difficulty breathing, breathlessness, respiratory distress, inability to get a "good breath in," rapid or shallow breathing, and sensations of choking or suffocation (Christopher & Morris, 2010; Hicks et al., 2008; Hoyte, 2013; MacConnell et al., 2014; Scano, Stendardi, & Grazzini, 2005). Dyspnea can include an array of

perceptions including air hunger, respiratory load, and throat/chest constriction (Parshall et al., 2012; Scano et al., 2005). In individuals diagnosed with ELBD, reports of dyspnea can range from mild discomfort to severe respiratory distress. What is known of dyspnea in ELBD is that symptoms are episodic, with a sudden onset. It is not uncommon for these symptoms to elicit panic and fear of asphyxiation, where fear continues to perpetuate or worsen symptoms (Hoyte, 2013; Newman, 2003). Although dyspnea in and of itself is not an indicator of pathology, the language patients use to describe their dyspnea could help differentiate ELBD from other disorders, and could even be used to classify clusters of pathology within the ELBD spectrum (Intarakamhang & Wangjongmeechaikul, 2013). For example, *shortness of breath* could be more characteristic of ELBD while *breathlessness* could be a better indicator of exercise deconditioning or restrictive lung disease (e.g., COPD). This question can be pursued in later studies, once diagnostic criteria for ELBD have been more clearly established.

Additionally, quantifying the *intensity* of dyspnea through validated tools can help determine benchmarks for pathology, level of disability, and to assess treatment outcomes. Such quantification scales can be direct (e.g., symptomatic visual analog scales [VAS] that assess current levels of perceived symptoms during provocation challenge). Scales can also be indirect (e.g., psychophysical severity scale, such as the Dyspnea Index [DI]), addressing how dyspnea impacts activities of daily life (Crisafulli & Clini, 2010; Gartner-Schmidt et al., 2014). The DI is one of the only scales validated for the ELBD population. However, although this symptom-specific index is a good indicator of impact of ELBD on quality of life, it is not a good measurement tool to assess symptom severity *during* ELBD episodes. Conversely, the benefit to using a VAS is that it has been shown to represent physical exertion *in the moment*, and has strong linear relationships between levels of dyspnea and exercise intensity (Atiken, 1969; ATS, 1999;

De Torres et al., 2002; Foglio et al., 1999; Intarakamhang & Wangjongmeechaikul, 2013; Martinez et al., 1997; Ries, 2005). Although the VAS has been validated in various cohorts (e.g., COPD), its validity has not been explicitly tested in patients with ELBD. Therefore, the first specific aim of this dissertation was to confirm the validity of the VAS in patients with E-PVFM and provide benchmarks for comparisons with healthy athletic controls.

In addition to dyspnea, other ancillary symptoms thought to indicate ELBD have also been extensively reported across multiple domains of literature: noisy breathing (stridor), lightheadedness, syncope, paresthesia, dyspnea on expiration, throat/upper chest/accessory muscle tightness/tension, extrinsic/intrinsic laryngeal muscle tension, and other laryngeal-based behaviors and symptoms such as cough, throat clearing, globus sensation, dysphagia, or dysphonia (Balkissoon & Kenn, 2012; Christopher & Morris, 2010; Dunn, Katial, & Hoyte, 2015; Hoyte, 2013; Morrison & Rammage, 2010a; Vertigan, Gibson, et al., 2007). Interestingly, not all symptoms from this extensive list appear in all clinical cases, and reported patterns are somewhat specific to medical domain. Additionally, whether these ancillary symptoms are actually indicative of ELBD or reflect concomitant pathology (e.g., muscle tension dysphonia, chronic cough) remains unclear. Therefore, methods to categorize and quantify these various symptoms, in context of etiological theories, should be used to discriminate these pathologies. Methods involving the study of ELBD symptoms in the exercise-induced variant are described in Chapter 3.

2.2.3.2.3 Episodic triggers

One of the hallmarks of ELBD are their sudden, periodic, and transient nature when the larynx is exposed to provoking triggers. Triggers can be exogenous (outside the body) or endogenous (within the body). Exogenous triggers can be irritants from the surrounding environment (e.g.,

noxious fumes or chemicals, cigarette smoke, or perfumes) or they can be triggers relating to temperature or weather (e.g., dry air, cold temperatures, drastic changes in weather) (de la Hoz et al., 2008; Herin et al., 2012, 2012; Perkner et al., 1998). Exogenous triggers can also be psychological stimuli, related to the "state" of the individual's surrounding environment (e.g., stressful work or home environment) (Forrest et al., 2012; Gavin et al., 1998; Husein et al., 2008; Leo & Konakanchi, 1999; Nascimento et al., 2013; Selner et al., 1987). Endogenous triggers include physiological or systemic irritants (e.g., post nasal drip, laryngopharyngeal reflux, inflammatory diseases), psychogenic factors related to the individual's "trait" (e.g., depression, high arousal, anxiety), or sudden aerodynamic changes within the respiratory system (e.g., abnormally high negative inspiratory pressures) (Cukier-Blaj et al., 2008; Heatley & Swift, 1996).

The list of potential exogenous and endogenous triggers is extensive, and the types of stimuli that trigger episodes are specific to individuals. To complicate things further, precipitating factors that *initially* influence ELBD development may be different from those that perpetuate the condition. For example, individuals acutely exposed to a noxious irritant (e.g., debris at World Trade Center) can find themselves hyper-responsive to any number of dyspnea-inducing irritant provocations after the initial event (Rafael, Shohet, & Cohen, 2010). Christopher and Morris (2010) were the first to classify the host of ELBD triggers variably described within the literature under the umbrella *Periodic Occurrence of Laryngeal Obstruction* (POLO) into the following three categories: (1) exertion-induced, (2) irritant-induced, and (3) psychologically-associated. The POLO model recognizes the heterogeneous nature of triggers presenting across the ELBD population. The three categories under "Triggers" in the original comprehensive taxonomy framework—"Exertional, "Psychological" and "Irritant"—also correspond to the POLO model.

It is important to not the distinction between *acute* trigger stimuli reflective in the comprehensive taxonomy framework and the influence of concomitant or underlying etiological factors in ELBD, described in the Etiological Frameworks section (Section 2.3). Asthma as a disease process can be used to illustrate these differences. Just as with ELBD, asthma is *triggered* by any number of endogenous and exogenous stimuli. Triggers initiate acute (reversible) episodes of active lower airway obstruction (i.e., bronchoconstriction). However, the *underlying* mechanisms that predispose or *cause* asthma to occur in the first place are a complex combination of various systemic (e.g., genetic predisposition, obesity) and environmental (e.g., microbial exposure) factors that lead to chronic inflammation of the lower airways, even in the absence of triggers (Ege et al., 2011; Zhang et al., 2010). An individual whose asthma is *triggered* by stress, for example, most likely did not *develop* asthma from said stress. In other words, although stress can influence inflammatory processes, other underlying factors are most likely responsible for this inflammatory origin. Unlike in asthma, the underlying cause(s) in ELBD has not yet been determined. However, in the meantime, caution should be taken to not confuse trigger stimuli from mechanisms involved in underlying pathophysiology of this clinical presentation.

2.2.3.3 Updated Comprehensive Taxonomy Framework

Figure 2-11 is the updated comprehensive taxonomy framework in its entirety. Several modifications were made based on current knowledge from the previous literature review described in Section 2.2.3.2. The first addendum involves an updated approach to the study of laryngeal response patterns. A more systematic method involving splitting laryngeal dynamics by locus of obstruction, respiratory cycle (inspiration/expiration), and the type of muscle patterns may provide a more organized platform for quantifying patterns of laryngeal obstruction and identifying these patterns within different feature variants across the ELBD spectrum. A visual

representation of the updated format to the comprehensive taxonomy framework for the category "Laryngoscopic Findings" can be found in Figure 2-11.

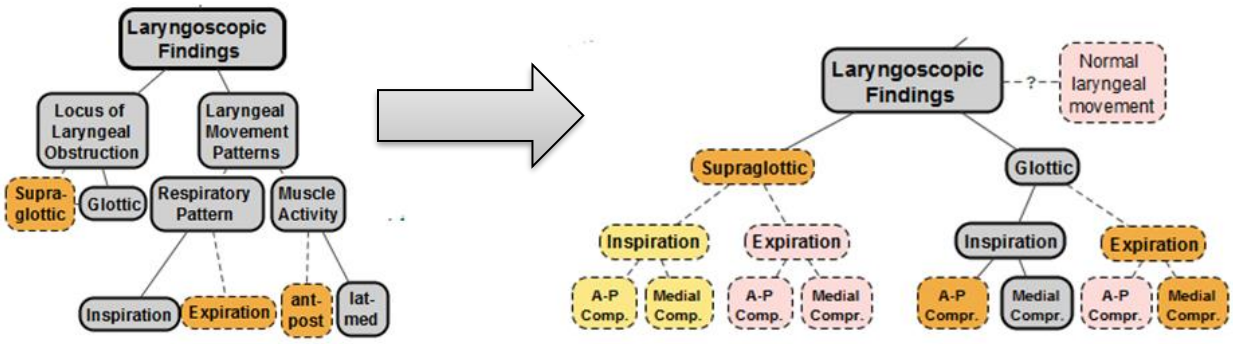


Figure 2-11. Laryngoscopic findings classification from the original comprehensive taxonomy framework (Left) and the proposed changes to the comprehensive framework (Right). Features common across the three models (ILS, DT, and POLO), represented in grey (solid) boxes, include inspiratory vocal fold adduction. Other variably reported features, represented in colored (dotted) boxes, include supraglottic medial and antero-posterior patterns (e.g., ventricular compression and arytenoid prolapse, respectively) and true vocal fold adduction on expiration. A-P comp. = antero-posterior compression.

The second addendum to the comprehensive taxonomy framework involved adding potential symptoms features indicative of ELBD to the previous list of features—lightheadedness/dizziness, limb paresthesia, syncope, systemic fatigue—across the three conceptual models. A schematic of how the symptoms category was updated in the comprehensive taxonomic framework is represented in Figure 2-12.

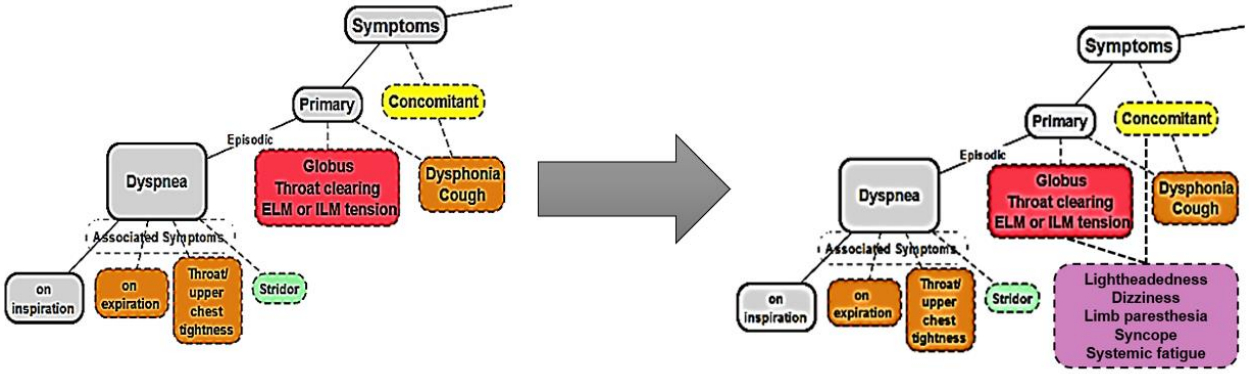


Figure 2-12. Symptoms from the original comprehensive taxonomy framework (Left) and the proposed changes to the symptoms category in the updated comprehensive framework (Right). Features common across the three models (ILS, DT, and POLO), represented in grey (solid) boxes, include episodic inspiratory dyspnea. Other variably reported features, represented in colored (dotted) boxes, include dysphonia, cough, globus sensation, throat clearing, perilaryngeal muscle tension, dyspnea on expiration, stridor, throat tightness, lightheadedness, dizziness, limb paresthesia, syncope, systemic fatigue. ELM = extrinsic laryngeal muscle. ILM = intrinsic laryngeal muscle.

The third addendum to the comprehensive taxonomy framework was in the classification of trigger categories. Each category was further divided into endogenous and exogenous factors that can trigger ELBD. This addition can help parse out endogenous mechanistic influences and contributory exogenous factors to more directly identify each of their contributions to trigger presentations. From a treatment management perspective, systematic identification of endogenous and exogenous influences encompassing trigger variants can guide personalized medicine in the future. A schematic of how the trigger category was updated in the comprehensive taxonomic framework is represented in Figure 2-13.

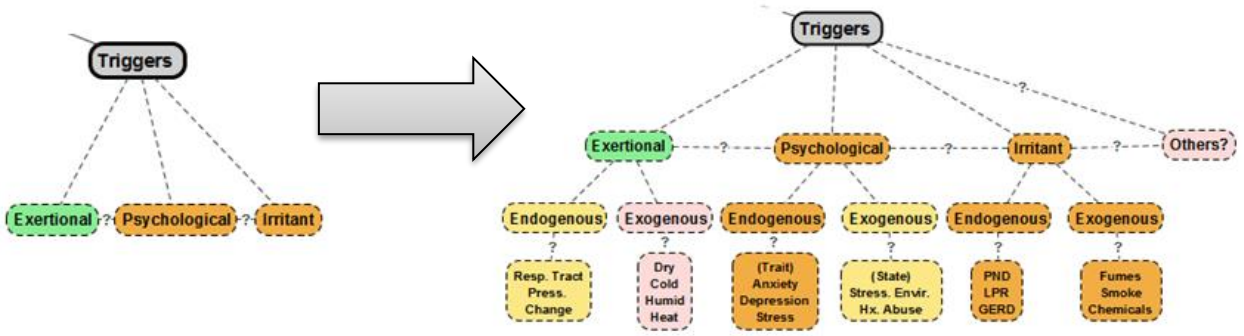


Figure 2-13. Triggers classification from the original comprehensive taxonomy framework (Left) and the proposed changes to the comprehensive framework (Right), further divided into endogenous and exogenous subcategories. Triggers across the three models (ILS, DT, and POLO) have been classified as exertional, psychological, and irritant. The "Triggers" category to the left of the arrow is the schematic representation in the original comprehensive taxonomy framework. The "Triggers" category to the right of the arrow is the updated version of the comprehensive taxonomy framework. Each trigger variant on the right can be further described as endogenous (e.g., high negative inspiratory pressures, temperament, reflux [GERD, LPR], and post-nasal drip [PND]), or exogenous (e.g., heat and humidity, stressful situations, and chemicals). PND = post-nasal drip. LPR = laryngopharyngeal reflux disease. GERD = gastroesophageal reflux disease.

Figure 2-14 is the schematic representation of the entire updated comprehensive taxonomy framework. The framework informed research questions and study design for the dissertation study. Because reported features in the literature are primarily based on descriptions of small sample sizes and expert opinion, the goal of the dissertation study was to prospectively identify participants with ELBD using the common features identified in the comprehensive framework and to measure pathological benchmarks using identified diagnostic indicators. The other goal was to assess the role of other reported auxiliary features to determine how they fit into one ELBD trigger variant—exercise-induced ELBD (E-ELBD)—using the comprehensive taxonomic framework. Identified features were then used to evaluate how variably presented features across different literature domains fit into the diagnosis of ELBD (or whether these features better reflect other concurrent pathology). Finally, the comprehensive taxonomy framework was used to study

the merit of two potential underlying mechanisms driving clinical expression in E-ELBD. These potential mechanisms—autonomic nervous system dysfunction and temperament (stress reactivity) are described in the final section of this chapter (Section 2.3).

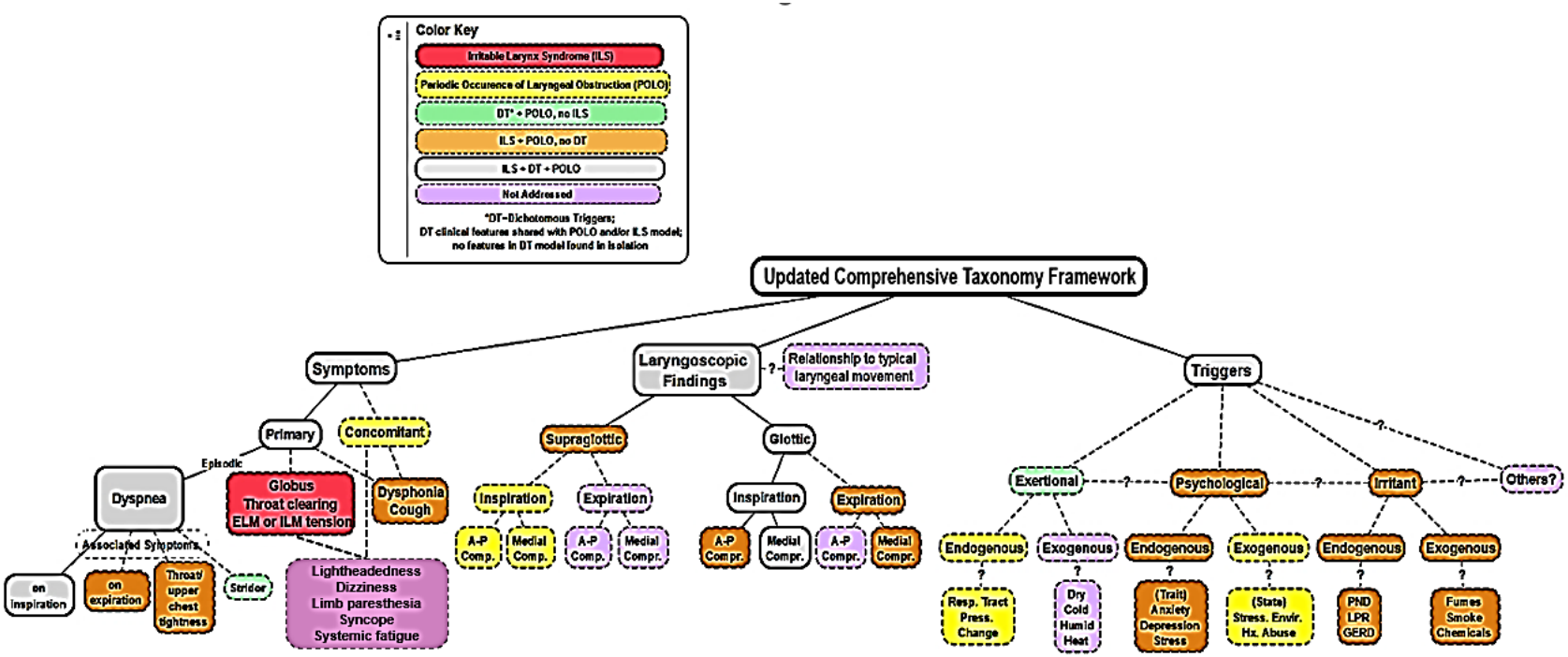


Figure 2-14. Updated comprehensive taxonomy framework. Based on the following three models: Irritable Larynx Syndrome, Dichotomous Triggers, and Periodic Occurrence of Laryngeal Obstruction and a comprehensive literature review. Grey (solid) boxes represent clinical features common across the three ELBD models (ILS, DT, and POLO). Colored (dotted) boxes represent feature discrepancies across models.

2.3 ETIOLOGICAL FRAMEWORKS

Mechanisms underlying dysfunctional breathing remain unclear. However, we can assume that clinical presentations of ELBD most likely involve some constellation of physiological, psychological, biomechanical, neurological, genetic, and immunological factors that interact and influence each other (Chaitow, Bradley, & Gilbert, 2013; Courtney, Greenwood, & Cohen, 2011; Gardner, 1996; Gimenez & Zafra, 2011; Johansson, 2013). Understanding what causes these clinical presentations is beneficial for several reasons. First, it can help identify individuals susceptible to developing ELBD. Second, it can be used to better identify individuals with the condition, streamline diagnostic procedures, and predict prognosis. Third, it can guide personalized therapeutic interventions. Although well-developed etiological hypotheses lack in the ELBD literature, three theories have been proposed: (1) Altered Autonomic Balance, (2) Primary Psychosomatic, and (3) Laryngeal Hyperresponsiveness. The latter two theories are described in the Future Directions Section (Section 6.3.2) as potential mechanisms underlying psychologically-associated and irritant-induced ELBD, respectively. A description of the autonomic balance theory, and one component of the psychosomatic theory—temperament—will be addressed in the following sections to set the stage for the proposed study's exploratory aims.

2.3.1 Autonomic nervous system dysfunction

The autonomic nervous system (ANS) is the primary driver for breathing (Undem et al., 1999). The ANS maintains homeostatic stability below the level of consciousness by controlling airway muscle tone, reflexes, blood flow, and secretions (Barnes, 1990, 1996; Baroody & Canning, 2003; Canning & Undem, 1994; Critchley, 2005; Hlastala & Berger, 2001; Loehrl et al., 2002; Martínez-

Lavín & Hermosillo, 2000; Mukhopadhyay et al., 2007; Noback et al., 2005; Weigand & Undem, 2012). The two subsystems of the ANS—the parasympathetic (PNS) and sympathetic (SNS) nervous systems—work together to regulate various cardiovascular functions such as heart rate and heart contraction/relaxation. The symbiotic relationship of these subsystems is especially critical during allostatic[11] activities such as exercise (Coote, 2010; Mador & Acevedo, 1991; Younes & Burks, 1985).

Specifically, with initiation of exercise, there is an immediate decrease in vagal tone associated with PNS inhibition, resulting in increased heart rate (Eryonucu, Bilge, Güler, & Uygan, 2000). Once heart rate reaches about 100 BPM, cardiac sympathetic fibers activate, causing increased left ventricle contraction and augmented stroke volume. This action yields up to a 39 (± 18) mmHg increase in systolic blood pressure (SBP). These patterns are then followed by further vagal withdrawal. Systolic blood pressure (SBP) is thought to be primarily mediated by the SNS during *vigorous exertion*, whereas heart rate (HR) results from sympathovagal balance in both submaximal and maximal exertion conditions (Coote, 2010; Eryonucu et al., 2000).

Post exertion, continued efficient sympathovagal balance is needed to return the body back to homeostatic baseline. The ANS helps the body recover via parasympathetic reactivation at about 44 (± 37) seconds post-exertion and sympathetic withdrawal at about 65 (± 56) seconds post-exertion (Pierpont & Voth, 2004). Sympathetic withdrawal results in vasodilation and a decrease in blood pressure (especially SBP), while simultaneous sympathetic withdrawal and parasympathetic reactivation reduces heart rate. The difference between heart rate at peak exercise and 2-minutes post-maximum exercise—referred to as *heart rate recovery* (HRR)—is thought to

[11] The process of regaining homeostatic stability after the body has been introduced to physiological or behavioral perturbations to the system.

be a robust indicator of the efficiency of this sympathovagal balance with exertive activity (Dishman et al., 2000; Eryonucu et al., 2000; Langdeau, Turcotte, Desagné, Jobin, & Boulet, 2000; Tunnicliffe, Hilton, Harrison, & Ayres, 2001). HRR latency has been shown to indicate a variety of morbidities including asthma, generalized anxiety disorders, and overtraining syndrome (among others) (Ayres & Gabbott, 2002; Dishman et al., 2000; Pierpont & Voth, 2004; Tunnicliffe et al., 2001). Beauchaine (2001) found inadequate vagal modulation in children prone to anxiety, and suggested these patterns may be indicative of emotional lability and increased fight/flight response, which can lead to, or at the very least be associated with, generalized anxiety disorders (Beauchaine, 2001). Figure 2-15 represents typical (average) SBP and HR responses and trends in healthy adolescent athletes (Al Haddad, Laursen, Chollet, Ahmaidi, & Buchheit, 2011; Becker, Silva, Moreira, & Victor, 2007; Buchheit et al., 2008; Muntner P, He J, Cutler JA, Wildman, & Whelton, 2004; Singh, Rhodes, & Gauvreau, 2008).

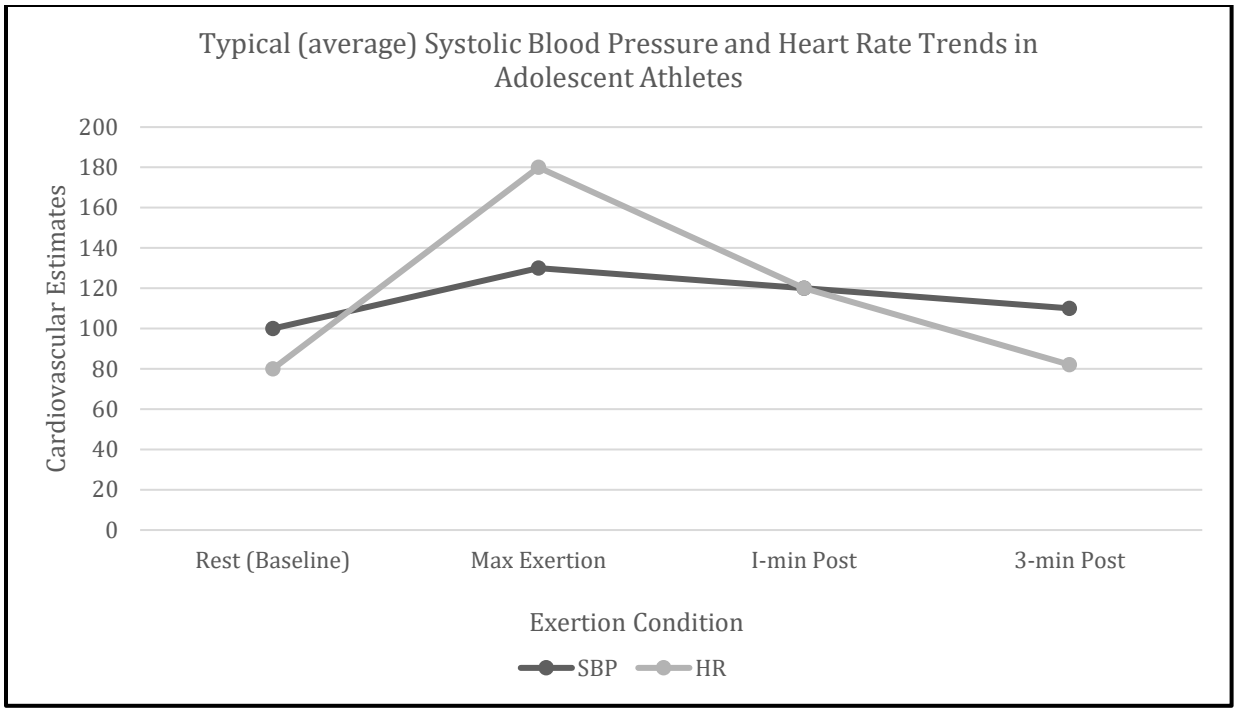


Figure 2-15. Trends in systolic blood pressure and heart rate responses in adolescent athletes. SBP = systolic blood pressure. HR = heart rate. Trends show an increase in SBP with rigorous (max) exercise and a gradual decrease with exercise cessation. Heart rate trends show a spike in HR at maximum exertion and a more pronounced decrease in recovery compared to SBP.

Although laryngeal-respiratory interactions are known to be mediated by the ANS for various biological functions including breathing, coughing, and swallowing, exactly how these interactions relate to laryngeal breathing pathophysiology is not well understood. In a brief editorial piece by Ayres and Gabbott (2002), the authors proposed ANS dysfunction correlates with ELBD, based on high prevalence of ANS dysfunction found in individuals with asthma. Additionally, recent studies have shown a positive correlation between increased intrinsic laryngeal muscle activity and heightened autonomic response to psychological stressors in healthy control subjects (Helou, 2014; Helou, Wang, Ashmore, Rosen, & Abbott, 2013). However, the

efficiency of sympathovagal balance in relation to the larynx has yet to be studied with exertion tasks, in general, or in the E-ELBD population, specifically.

Therefore, investigation into whether autonomic balance even plays a role in underlying pathophysiology driving ELBD clinical expression (and if so, what kind of sympathovagal balance patterns can be expected) is warranted. Table 2-3 is a summary of five hypothetical laryngeal-autonomic relationship outcomes.

Table 2-3. Laryngeal-Autonomic System Hypotheses of Underlying Potential Study Outcomes. Hypotheses stem from work by Ayres & Gabbott, 2002; Dishman et al., 2000; Helou, 2014; Helou et al., 2013; Kreher & Schwartz, 2012; Lehmann, Foster, Dickhuth, & Gastmann, 1998; Pierpont & Voth, 2004.

AUTONOMIC FUNCTION		LARYNGEAL ACTIVITY	CARDIO-VASCULAR OUTCOMES FOR EXERTION	CLINICAL PRESENTATION EXAMPLES
ANS output	*Underlying Mechanism(s)*			
I. SNS < PNS	*Hypothesis 1:* attenuated/blunted SNS response; normal PNS response	↑vagal tone = ↑ILM adductor activity (TA, IA, LCA)	Blunted ΔSBP[12] Normal HRR	Adrenergic depletion; overtraining syndrome
	Hypothesis 2: ↑SNS response; ↑↑increase PNS response		Increased ΔSBP Accelerated HRR	Vagal overcompensation syndrome; 1° Depression & 2° Anxiety Disorder
II. SNS > PNS	*Hypothesis 3:* ↑SNS response; normal PNS response	↓vagal tone = ↓ILM abductor activity (PCA)	Increased ΔSBP Normal HRR	Anxiety/Panic Disorders
	Hypothesis 4: ↓SNS response to exertion; ↓↓attenuated/blunted PNS response		Blunted ΔSBP Slow HRR	Mood (depression) Disorders
	Hypothesis 5: ↑↑↑SNS response; ↑↑increase PNS response (vagal overcompensation)		Increased ΔSBP Normal or accelerated HRR	1° Anxiety Disorder & 2° Depression

[12] ΔSBP determined by the magnitude difference between rest (baseline) and exercise SBP.

2.3.2 Personality, Temperament, and Stress Reactivity

There has been little studied on associations between temperament, mental/behavioral disorders, and ELBD, despite frequent references to their connection (Al-Alwan & Kaminsky, 2012; Anbar, 2012; Appelblatt & Baker, 1981; de la Hoz et al., 2008; Dunglison, 1842; Kuppersmith, Rosen, & Wiatrak, 1993; McGrath, Greenberger, Zeiss, & others, 1984; Morris, Oleszewski, Sterner, & Allan, 2013; Nagai, Yamaguchi, Sakamoto, & Takahashi, 1992; Niven, Roberts, Pickering, & Webb, 1992; Patterson et al., 1974; Pitchenik, 1991; Richards-Mauzé & Banez, 2014; Ringsberg, Löwhagen, & Sivik, 1993; Rothe & Karrer, 1998; Smith, Darby, Kirchner, & Blager, 1993; Smith, 1983). Unfortunately, most of the literature in this domain is riddled with bias, and claims of interconnections between psychopathology and ELBD are generally couched in observational case series, descriptive case reports, and expert opinion. One literature review on ELBD (consisting of case reports and case series) alleged ELBD was "associated with severe psychosocial stress and difficulties with modulation of intense emotional states." Findings were attributed to the "higher" prevalence of a variety of "psychological disturbances" within the ELBD population. However, a direct comparison of psychological prevalence between individuals with ELBD and the general public, generally suggests otherwise (see Table 2-4 for details).

Table 2-4. Prevalence of Psychological Disturbances in The General Population Compared to The ELBD Population.

Psychopathology	Prevalence in general population[13]	Prevalence in ELBD population[14]
Conversion disorder[15]	0.5%	12%
Anxiety disorder	11-17%	11%
Histrionic and other personality disorders	15%	6%
Family/school conflicts	7%	4%
Depression	4-7%	4%
Psychosomatic disorders	2%	2%
Factitious disorders	0.7-2.0%	2%
Somatization/somatoform disorders	0.2-2%	1%

The bias in the belief psychogenic conditions cause ELBD is especially prevalent in the literature on exercise-induced ELBD, particularly with adolescent *female* athletes. In a case study by Maschka and colleagues (1997), the cause of exercise-induced ELBD in a female athlete was attributed to an underlying "non-organic somatization/conversion disorder" due to her "high achieving, competitive, and mildly anxious" nature (Maschka et al., 1997). However, anyone who has interacted with the adolescent female athletic population can speak to their similar temperament as that described by Maschka and colleagues. Yet, not all female athletes develop somatization disorders or E-ELBD. Further study of causal relationships (if they do exist) addressing the merit of poorly-controlled temperament (e.g., Type A, anxious, neurotic, highly

[13] Sources: Carter, Briggs-Gowan, & Davis, 2004; deGruy, Columbia, & Dickinson, 1987; Fliege et al., 2007; Gordon, 1987; Grant et al., 2004; Lichstein, 1986; Oyama, 2011; Somers, Goldner, Waraich, & Hsu, 2006.
[14] Results of literature review by Leo and Konakanchi, 1999
[15] ICD-10 classifies conversion disorders as *dissociative* disorders while DSM-IV classifies conversion as *somatoform* disorders. Interestingly, Leo and Konakanchi found "conversion" disorder in 12% of individuals with ELBD and only 1% with "somatoform" disorder. The 11% discrepancy in what appears to be the same diagnosis is perplexing.

stress reactive) and psychogenic correlates (e.g., somatization/conversion disorder, anxiety disorders) as a mechanism underlying E-ELBD is warranted. To address the validity of this theory, the etiology of E-ELBD as psychogenic in nature was also explored in the dissertation study.

3.0 STUDY DESIGN

The goal of the study was to identify clinical features and underlying mechanisms in one type of ELBD, Exercise-induced ELBD (herein referred to as E-ELBD). Primary features of dyspnea severity and glottal configuration, informed by the comprehensive taxonomy framework addressed in Chapter 2 were used to identify pathological benchmarks between adolescent athletes with and without E-ELBD. The prevalence of other (auxiliary) features, previously implicated in ELBD, were also identified and compared between the two athletic groups to determine which of these features were *indicative* of E-ELBD. Finally, the merit of two potential mechanisms underlying the E-ELBD variant—autonomic dysfunction and stress reactivity (temperament)—was investigated to determine their role for future investigations. The study design was first validated in individuals with the E-ELBD variant. The rationale for this decision was that this variant is thought to involve the most homogenous group of the trigger variants (exercise, irritant, psychological), thereby reducing the possibility of confounding variables in study designs. Future investigations will apply validated study methods from this dissertation study to other ELBD trigger variants (i.e., irritant-induced, psychosomatically-associated).

3.1 SPECIFIC AIMS

3.1.1 Primary Aims

The primary aim (SA1) was to quantify magnitude differences in glottal configuration at height of inspiration and perceived dyspnea from rest to exercise in athletic adolescents diagnosed with E-ELBD, compared to healthy athletic adolescent volunteers without complaint of breathing affecting athletic performance.

3.1.1.1 Inspiratory glottal configuration

SA1(A): Quantify magnitude of change in true vocal fold adduction (anterior glottal angle) on inspiration from rest to exercise in adolescents diagnosed with E-ELBD, compared to findings for healthy athletic volunteers of the same age range.

H_1: An exertion by group interaction will be shown. Participants with E-ELBD will show a significant change (increase) in inspiratory vocal fold adduction from baseline rest to exercise conditions, compared to healthy athletic volunteers.

H_0: No significant differences in magnitude of change from rest to exercise conditions will be shown between E-ELBD and control groups.

3.1.1.2 Self-reported dyspneic symptoms

SA1(B): Quantify perceived dyspnea at rest and with exercise challenge and compare scores in the same subjects as for SA1(A).

H_1: Participants with E-ELBD will have a statistically significant increase in dyspnea severity from baseline (rest) to exercise conditions compared to control participants.

H_0: No significant difference will be shown for dyspnea severity ratings on the 0-100 VAS.

3.1.2 Secondary Aims

A secondary aim was to identify ancillary laryngeal respiratory dynamic patterns and perceived symptoms indicative of E-ELBD and determine quantitative benchmarks for pathology, as means to improve diagnostic specificity.

3.1.2.1 Supraglottic laryngeal-respiratory kinematics

SA2(A): Identify and quantify patterns of ancillary supraglottic laryngeal dynamics (arytenoid prolapse, epiglottic collapse, ventricular compression) on a 0-3 severity scale and expiratory glottal responses using anterior glottal angles, and determine group differences.

H_1: Arytenoid prolapse will be found in one-third of individuals diagnosed with E-ELBD in the exercise challenge. This hypothesis is informed by a retrospective study showing that 32% (7/22) of adolescent participants with E-ELBD showed "paradoxical" arytenoid movement (Powell et al., 2000; Bittleman et al., 1994; Christensen et al., 2010; Christopher & Morris, 2010; Fahey et al., 2005; Atsushi Nagai, Kanemura, & Konno, 1992).

H_0: Prevalence of arytenoid prolapse will be similar between E-ELBD and control groups during the exercise challenge. These patterns could be due to a combination of negative inspiratory supraglottic pressures (i.e., Bernoulli Effect, Venturi Effect) and systemic fatigue and may not be

indicative of E-PVFM. Although arytenoid prolapse has been seen in individuals with E-ELBD, laryngeal movement in athletic cohorts without the condition has been little studied.

3.1.2.2 Ancillary self-reported symptoms.

SA2(B): Identify auxiliary symptoms most prevalent in the E-ELBD cohort from a list of potential symptoms (see Section 3.1.2.2 for complete list), quantify severity of these features, and compare severity ratings between individuals with E-ELBD to those without the condition.

H_1: Individuals with E-ELBD will report stridor more often than athletic adolescent volunteers, as this auxiliary symptom has been suggested to be more prevalent in E-ELBD than other ELBD variants (Christopher & Morris, 2010; Hicks et al., 2008; Powell et al., 2000). Christopher and Morris (2010) suggested the source of stridor is vibration of the corniculate cartilages with increased inspiratory supraglottic pressures, which can occur with rigorous physical activity. Hypotheses regarding other findings again, at this point, remain more speculative.

H_0: No significant difference will be found in the prevalence of stridor between individuals with E-ELBD and athletic volunteers.

3.1.3 Exploratory Aims

The exploratory aim (SA3) will investigate two previously proposed potential mechanisms involved in E-ELBD pathoetiology in the ELBD literature: altered autonomic balance (Ayres & Gabbott, 2002; Balkissoon & Kenn, 2012; Helou et al., 2013) and stress reactivity (temperament) (Al-Alwan & Kaminsky, 2012; Ferris et al., 1998; Husein et al., 2008; Kaufman et al., 2004; Lund

et al., 1993; Nayar et al., 2003; Niggemann, 2010; R. Patterson et al., 1974; Powell et al., 2000; M. S. Smith, 1983; H. S. Snyder & Weiss, 1989).

3.1.3.1 Altered autonomic balance.

SA3(A): Investigate autonomic (sympathovagal) balance in adolescents with E-ELBD and athletic volunteers using two proxy measurements of autonomic function: magnitude of change in systolic blood pressure from rest to exercise (ΔSBP) and heart rate recovery from maximum exertion with exercise challenge to 2-minutes post-maximum exertion (HRR).

H_1: Any of the following outcomes could occur: (1) ΔSBP (magnitude change based on SBP at rest and SBP during maximum exertion) will be significantly blunted in the E-ELBD group (compared to athletic volunteers) during exercise due to attenuated SNS response or slow PNS withdrawal; (2) ΔSBP will be significantly greater in the E-ELBD group during exercise due to substantial increase in SNS activation, likely to occur in conjunction with heightened sympathetic response to provoked ELBD episode; (3) HRR will be significantly accelerated in the E-ELBD group during recovery due to increased vagal tone (or overall sluggish SNS response, also seen with blunted SBP response during exertion); (4) HRR will be significantly lower post-exertion in the E-ELBD group due to sluggish PNS response in reactivation (or overall heightened SNS response, also seen with greater SBP response during exertion).

H_0: No significant differences in ΔSBP or HRR between patients with E-ELBD and athletic volunteers, suggesting normal sympathovagal balance in the E-ELBD group.

3.1.3.2 Personality and stress reactivity (temperament).

SA3(B): Investigate temperament differences across individuals with E-ELBD and healthy athletic volunteers using the Fear Subscale of the Early Adolescent Temperament Questionnaire – Revised (EATQ-R) (see *Appendix B: Early Adolescent Temperament Questionnaire – Fear Subscale*).

H_1: A statistically significant difference on the Fear Subscale of the EATQ-R will be shown between the two groups, suggesting greater proclivity for stress reactivity and trait anxiety in the E-ELBD group.

H_0: Differences in the EATQ-R Fear Subscale will not reach statistical significance between the two groups. This null hypothesis is based on the concept that competitive athletic adolescents within this age range, in general, share similar dispositions and temperaments (e.g., proclivity for perfectionism) (Bartulovic, Young, & Baker, 2017; Hill & Madigan, 2017; Weinberg & Gould, 2011), and both control and E-ELBD participants will be athletes.

3.2 STUDY VARIABLES

3.2.1 Independent Variables

Independent variables remained the same across all three study aims. There were two independent variables (1) and (2), each with two distinct levels (a) and (b). The first independent variable was (1) *level of exertion* with the following two levels, (a) baseline (rest) and (b) maximum exertion (exercise challenge). The second independent variable was (2) *group* with two levels, (a) patients diagnosed with E-ELBD and (b) athletic adolescent volunteers without breathing complaints.

3.2.2 Dependent Variables

3.2.2.1 Primary variables

Inspiratory glottal configuration. The dependent variable for the first primary aim SA1(A) was *anterior glottal angle* (Figure 3-1). Anterior glottal angle estimates were used to quantify glottal configuration (aperture) during inspiration. Measurements from digital still images, acquired from dynamic videoendoscopic examinations, were taken at the height of inspiration, immediately prior to the start of expiration during laryngoscopy (see *Appendix C: Anterior Glottal Configuration Instructions for Raters* for details).

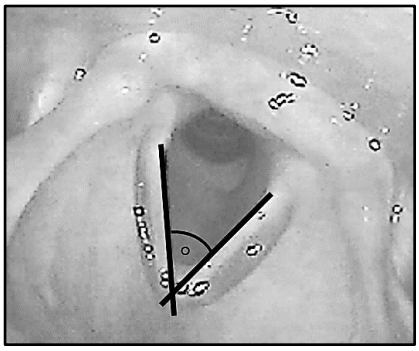


Figure 3-1. Anterior glottal angle measurements

Self-reported dyspneic symptoms. The dependent variable for the second primary aim SA1(B) was *inspiratory dyspnea severity*, based on self-reported symptom ratings at (a) baseline (rest) and in (b) maximum exercise conditions. Severity was determined using a 0-100 continuous visual analog scale (VAS) (see *Appendix D: Visual Analog Scale Perceptual Ratings* for details).

3.2.2.2 Secondary variables

Supraglottic laryngeal kinematics. There were 4 dependent variables for the first secondary aim SA2(A). Variables were magnitude of airway obstruction caused by (1) arytenoid prolapse (DV1),

(2) epiglottic collapse (DV2), (3) ventricular (false) fold compression (DV3), and (4) *expiratory* vocal fold adduction (DV4). The selection of these variables was based on literature review and comprehensive taxonomy framework (Shembel et al., 2017). All four parameters were assessed based on visual inspection of laryngoscopic videos acquired during both baseline (rest) and maximum exertion (exercise challenge) conditions. Ratings were conducted by seven naïve raters blinded to group and condition. Years of experience with laryngoscopy examination interpretation ranged from 3 to 20 years amongst the raters. The first three DVs (DV1-3) were each rated on a 0-3 scale as detailed in Table 3-1. DV4 was measured using anterior glottal angle measurements, mentioned previously with the first primary aim (*c.f.,* Section 3.1.1.1) (see *Appendix E: Supraglottic Movement Instructions for Raters* for details)

Table 3-1. Rating System for Supraglottic Laryngeal Kinematics

Obstruction Type	0	1	2	3
Arytenoid prolapse (DV1)[1]	Expected maximal abduction of the aryepiglottic folds with no visible medial rotation (top of cuneiform tubercles pointed vertical or slightly lateral)	Visual medial rotation of the cranial edge of the aryepiglottic folds and tops of the cuneiform tubercles	Further medial rotation of the cuneiform tubercles with exposure of the mucosa on the lateral sides of the tubercles	Medial rotation until near horizontal position of the cuneiform tubercles and tops of the cuneiform tubercles move towards the midline
Epiglottic Collapse (DV2)[2]	Petiole and purslane of the epiglottis hugs the tongue	Epiglottis between 0-45°	Epiglottis between 45-90°	Epiglottis over 90°
Ventricular (False) Fold compression (DV)[3]	Absent	1/3 of the true vocal folds covered	2/3 of the true vocal folds covered	True vocal folds completely hidden

[1]Validated by Maat (2011); [2]validated by Catalfumo et al., (1998); [3]validated by Schonweile et al (1998)

Ancillary self-reported symptoms. The second secondary aim involved dependent variables based on additional symptoms implicated in ELBD using the comprehensive taxonomy framework and literature review as a guide (Shembel et al., 2017):

Chest tightness
Cough
Dysphagia (swallowing complaints)
Globus sensation
Lightheadedness/dizziness
Limb paresthesia
Shortness of breath with expiration
Shortness of breath with inspiration
Stridor (noisy breathing)
Syncope
Systemic fatigue
Throat clearing
Throat tightness/constriction
Voice complaints (dysphonia/hoarseness)

The most common features reported in the E-ELBD cohort were identified and their respective severities were rated on a 0-100 continuous visual analog scale at (a) baseline (rest) and (b) maximum exertion (exercise challenge) conditions. All participants were asked to rate each of the following symptoms:

(1) expiratory dyspnea (How difficult is/was it to breathe out? [DV1])

(2) stridor ("How noisy was/is your breathing in" [DV2])

(3) throat tightness ("How tight was/is your throat?" [DV3])

Baseline ratings were taken during baseline laryngoscopy; exercise ratings were acquired retrospectively immediately after the exercise challenge to ensure safety of participants pedaling on the cycle trainer and to maximize exertion levels.

3.2.2.3 Exploratory variables

3.2.2.3.1 Altered autonomic balance.

The first exploratory aim had two dependent variables. The first was *magnitude of SNS response* (ΔSBP), determined by the difference between systolic blood pressure (SBP) measurements at baseline (rest) and during maximal exertion (exercise challenge) conditions. The second was *efficiency of PNS response*, determined by heart rate recovery (HRR), calculated as the difference between heart rate taken at maximum exertion (during exercise challenge) and 2 minutes after strenuous pedaling on the stationary trainer had been terminated.

It is important to note SBP and HRR parameters were not measuring *pure* SNS and PNS responses, respectively. Instead, the SNS and PNS work in conjunction for both SBP and HRR parameters. What was actually being measured was the *overriding* autonomic subsystem's output. Specifically, during rigorous physical activity SNS should prevail over the PNS as the SNS increases and PNS withdraws. However, there is still some PNS activity present during exercise to control beat-by-beat heat rate variability. Conversely, during recovery, the PNS should prevail over the SNS, although some SNS activity may still be present. In cases where there is slow SNS reactivity or sluggish PNS withdrawal with exercise, the SBP *output* during the exercise challenge will be lower than expected. Latent HRR *output* post-exercise is suggestive of either sluggish SNS withdrawal or slow PNS reactivation response once the participants stop pedaling on the stationary bike. With that in mind, the noted measurement outcomes for SA3(A) identified whether there was *some degree* of sympathovagal imbalance or inefficiency. However, the measures did not afford exact information on the instigating subsystem(s) of said inefficiency (i.e., SNS, PNS, or both). More intricate and invasive methods or use of animal models are required to identify specifics of

autonomic balance. If some degree of inefficiency or imbalance is demonstrated, more involved methods warrant future study, but did not lend themselves to exploration in the present study.

3.2.2.3.2 Stress reactivity (temperament)

The *Fear* Subscale on the Early Adolescent Temperament Questionnaire – Revised (EATQ-R) represented the dependent variable. The EATQ-R is a psychometric self-reported questionnaire that assesses excitability, emotionality, arousability, and self-regulation in children and adolescents. Each of the 11 subscales of the EATQ-R are thought to represent a subset of temperament constructs. Measures of temperament were chosen for this study aim since the concept of temperament has been linked to the development of psychopathological syndromes in general (Muris et al., 2009; Muris and Ollendick 2005; Nigg 2006). The subscale *Fear* targets the "unpleasant affect related to anticipation of the distress" (e.g., "I worry about getting into trouble") (Capaldi & Rothbart, 1992; Muris & Meesters, 2009). Previous studies have shown this subscale is a good indicator of stress-reactivity and is associated with higher levels of anxiety (Muris & Meesters, 2009).

3.3 PARTICIPANTS

The study was conducted with adolescent athletes, as E-ELBD is most commonly seen in physically active juveniles (Abu-Hasan et al., 2005; Al-Alwan & Kaminsky, 2012; Guglani, Atkinson, Hosanagar, & Guglani, 2014; H. Johansson et al., 2015; Landwehr et al., 1996; Mahut et al., 2013; Røksund et al., 2009; Tilles, 2010; Tilles, Ayars, Picciano, & Altman, 2013). Recruitment of a homogenous cohort helped minimize variance and increase internal validity,

which was especially important for the assessment of autonomic and temperament parameters (SA3). Two groups of participants between the ages of 12 and 18 years were recruited. The first group (experimental group; E-ELBD) were individuals who presented to the Voice and Speech Laboratory at the Massachusetts Eye and Ear Infirmary (MEEI) with complaints of atypical inspiratory dyspnea on exertion resulting in diminished athletic performance and who scored more than a 10 out of 40 on the Dyspnea Index, a symptom severity questionnaire previously validated in individuals with upper airway breathing pathology. The second group (healthy control group; HC) had no complaints of atypical exertional dyspnea over the past 6 months. The latter group was recruited from sports teams and local schools in the greater Boston region.

3.3.1 Sample Size

The *original* target sample size, prior to the start of enrollment, was n = 50 participants who satisfied inclusion criteria and who would complete the entire protocol (25 E-ELBD and 25 healthy controls). These numbers were based on power analysis, according to which 46 participants (23 E-ELBD and 23 healthy controls) were needed to provide 80% statistical power to detect a clinically significant difference between dyspneic symptom severity parameters (VAS), using Analysis of Variance (ANOVA) with an alpha level of 0.05 (Cohen's $d = 0.4$). This target sample size was thought to be feasible as there was report, based on an electronic medical database, of over 125 patients ages 12-18yo with laryngeal breathing disorders seen annually at the Massachusetts Eye and Ear Infirmary. The original estimated attrition was as follows: on average, 100 patients (80%) who received a formal diagnosis of E-ELBD typically consent to participation in research protocols of this type (MEEI database, unpublished data). An estimated 30-40 out of 100 patients (30-40%) with an E-ELBD diagnosis would have concomitant asthma that was not

well-controlled, characterized as a predicted FEV1 < 80% (Christopher & Morris, 2010; Hicks et al., 2008; Hoyte, 2013), an exclusion criterion for the present study. The projected 60-70 possible E-ELBD participants for recruitment made the targeted enrollment sample size of n = 50 in the E-ELBD group (and n = 35 in the control group), with a targeted final sample size of n = 25 in each group, feasible. The flowchart in Figure 3-2 illustrates the projected enrollment sample size, taking into account various factors that could cause attrition.

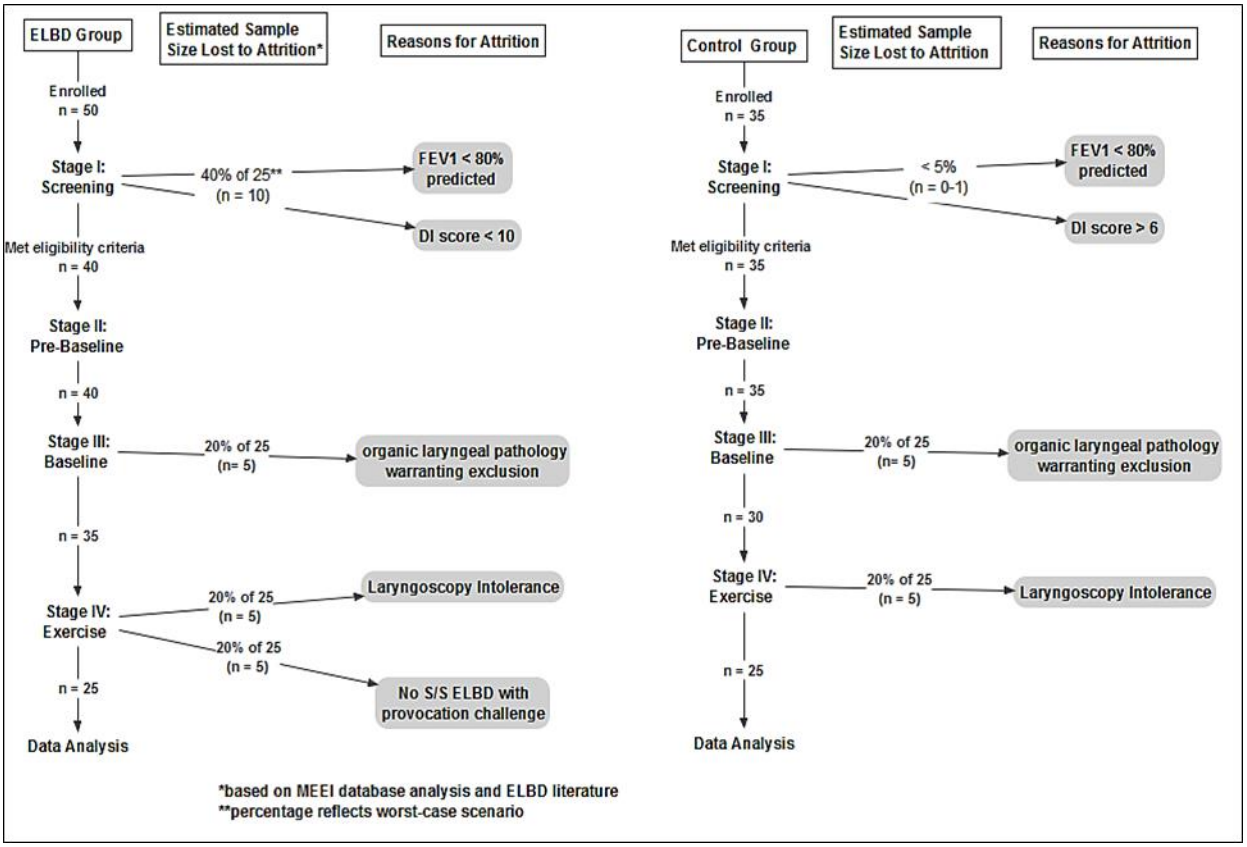


Figure 3-2. Original estimated enrollment and attrition flowsheet.

Unfortunately, available patients for recruitment in the E-ELBD (experimental) group were vastly fewer than anticipated (~20 per year in 2016-2017 versus ~100 per year in previous years) for unknown reasons. In an attempt to improve recruitment, local physicians were contacted

once a week to remind them of potential referrals for the study. Flyers and advertisements were reposted around MEEI and the surrounding areas weekly. Athletics directors and coaches across 35 different middle and high schools in the New England region were contacted via phone and email. Local Boston Craigslist ads were updated biweekly. And previous cancellations and no-shows were contacted for initial consultation and potential study recruitment at the Voice and Speech Laboratory at MEEI. However, recruitment continued to be substantially less than anticipated due to low patient referrals with suspected E-ELBD. Therefore, interim power analysis on n = 11 in the E-ELBD group and n = 13 in the control group was run in mid-June 2017 (8 months after the enrollment period began) using data on the primary outcome variables[16] to determine whether the current sample size was sufficiently powered. The interim (second) power analysis showed the current n = 24 sample size to be enough to achieve the statistical power needed to stop enrollment (total needed for main effect: n = 6; total needed for interactions: n = 12). Therefore, enrollment was discontinued at the end of the targeted recruitment period in the beginning of July 2017 with a total of n = 27 participants recruited (n = 13 E-ELBD; n = 14 control).

Of note, although the study was sufficiently powered for the primary aims, it was not powered for the autonomic parameters, to which 788 participants (394 E-ELBD and 394 healthy controls) were needed to provide 80% statistical power to detect a clinically significant difference between magnitude of change in systolic blood pressures using independent *t* tests with an alpha level of 0.05 (Cohen's $d = 0.2$). For the 2-minute heart rate recovery parameter, 352 total participants (176 E-ELBD and 176 healthy controls) would have been needed to provide 80%

[16] Based on 2x3 mixed-model ANOVA: IV1: group (E-ELBD, control); IV2: condition (pre-baseline, baseline, exercise); DV1: inspiratory dyspnea severity (VAS) and DV2: anterior glottal angle.

statistical power to detect a clinically significant difference between magnitude of change in systolic blood pressures using independent t tests with an alpha level of 0.05 (Cohen's $d = 0.3$).

3.3.2 Inclusion Criteria

All participants had to be adolescents (ages 12-18yo) who exercise regularly (at least 40 min 3x/week).

Inclusion criteria specific to E-ELBD group. Any participant who presented to the clinic reporting atypical dyspnea during exertion and associated decrements in athletic performance for more than 2 weeks prior to presentation was considered for the study. Participants in the experimental group also had to score at least a 10 out of 40 on the *Dyspnea Index* (score of 8 or more has been shown to be significant for E-ELBD in a previous study [De Guzman V et al., 2014]).

Inclusion criteria specific to healthy control group. In addition to meeting general inclusionary criteria, participants in the control group had to have no symptoms of atypical dyspnea over the past 6 months and had to score less than 7 out of 40 on the *Dyspnea Index*.

3.3.3 Exclusion Criteria

Table 3-2 includes a list of general exclusion criteria across the two groups, with rationales for exclusions provided. In addition, for the E-ELBD group *only*, data was excluded from analysis if there was absence of signs or symptoms of ELBD, either at baseline (e.g., "twitchy" laryngeal responses to endoscope in laryngeal vestibule) or an acute ELBD attack with exercise provocation challenge at maximum exertion. Positive E-ELBD provocation was based on participant report of symptoms they typically experienced with their athletic performance on the exercise trainer

(indicated by a "thumbs up" sign) and concurrent "atypical" glottic or supraglottic responses. Participant eligibility was determined by two licensed Speech-Language Pathologists.

Table 3-2. General Exclusion Criteria and Rationale for Exclusion

EXCLUSION	RATIONALE
(1) Developmental or cognitive disorder precluding ability to follow direction or read instructions	Participants will need to be able to comprehend questions on the DI and EATQ-R[17] Fear Subscale questionnaires and to follow directions in rating exertion perception with the physical exertion scale. Additionally, inability to fully understand the exercise laryngoscopy protocol can put participants at risk for overexertion or injury.
(2) Behavioral disorder that would disrupt study protocol or potentially affect outcome parameters (e.g., attention-deficit/hyperactivity disorder [ADHD], oppositional defiant disorder [ODD]).	Various studies have correlated autonomic under-arousal with behavioral disorders. For example, a study by Crowell et al., 2006 showed children with ADHD and ODD exhibited fewer electrodermal responses, lengthened cardiac pre-ejection periods, and heart rate changes suggestive of abnormal levels of parasympathetic withdrawal without sympathetic contributions. Therefore, behavioral disorders will be excluded to reduce a potential confound in autonomic function parameters in SA3(A). Behavioral disorders could also skew temperament parameters in SA3(B). Last, disruptive behaviors could put participants at risk for injury from the exercise protocol or could confound severity rating outcome parameters.
(3) Neuromuscular disorders affecting the respiratory or phonatory system (e.g., ALS, Myasthenia Gravis)	Neuromuscular disorders affecting laryngeal/respiratory systems could have a negative influence on laryngeal movement or laryngeal-pulmonary coordination, and could affect laryngeal configuration, symptom perception, or autonomic response parameters (SA1-SA3).
(4) Supralaryngeal anatomical defects impeding airflow	Changes in airflow from supraglottic obstruction could influence laryngeal movement and confound laryngeal configuration parameters (SA1[A], SA2[A]).
(5) Cardiovascular conditions/disorders (e.g., hypertension)	Cardiovascular conditions can influence SBP and HR measurements (SA3[A]) and moreover, put subjects at risk during exercise.

[17] DI = Dyspnea Index; EATQ-R = Early Adolescent Temperament Questionnaire – Revised.

Table 3-2 (Continued)

(6) Obstructive pulmonary disorders (not well-controlled)	Disorders such as not well-controlled asthma can confound laryngeal configuration parameters (SA1[A]; SA2[A]). Studies have shown the glottis narrows when air is trapped within the alveoli, as is the case in individuals with obstructive lung disease, especially during the exhalatory respiratory phase (Collett, Brancatisano, & Engel, 1986; England, Ho, & Zamel, 1985; Hicks et al., 2008; Higenbottam, 1980; Hoyte, 2013; Jamilla et al., 2000; Kenn & Balkissoon, 2011; Martin et al., 1987; O'Donnell, Sanii, Anthonisen, & Younes, 1987; Patterson & O'Connell, 1994). These laryngeal findings should not be present as long as the asthma or other obstructive pulmonary condition is controlled with corticosteroids or other inhalers (well-controlled obstructive disease categorized as FEV1 > 80% predicted).
(7) Use of the following medications: (a) anti-hypertensive, (b) cardiovascular, (c) psychotropic	These classes of medications have all been shown to influence sympathetic nervous system response (Chernow, Zaloga, Lake, Coleman, & Ziegler, 1984; Del Colle et al., 2007; Iwamoto et al., 2012).
(8) Identifiable (organic) vocal fold pathology occluding more than a 1/3 of the airway (e.g., lesions, nodules), found on laryngeal examination	Organic pathology occluding more than a third of the airway could influence configuration of the larynx or could increase laryngeal configuration measurement errors by raters (SA1[A]; SA2[A]).
(9) Intolerance to flexible nasoendoscopy or history of adverse response to over the counter nasal decongestants	All participants must tolerate the flexible laryngoscope and Afrin (or other nasal decongestant medication) to reduce discomfort of laryngoscopy in order to visualize the larynx for off-line laryngeal signs analysis (SA1[A]; SA2[A]). Moreover, a history of adverse response to nasal decongestants would put the participant at risk for potentially serious health consequences.

3.3.4 Recruitment and Informed Consent

Plans for recruitment. Patients with suspected E-ELBD were recruited for the experimental group from the Voice and Speech Laboratory at the MEEI during routine clinical care. Potential participants presenting with symptoms of E-ELBD were approached by the PI or another Speech-Language Pathologist at the initial consultation appointment. Control participants, recruited from

local sports teams and schools in the New England region, were consented by the PI at the time they presented to the clinic for possible participation. Advertisements (e.g., study brochures and flyers) were used to recruit participants, as needed. Prior to their initial visit to the clinic, all potential participants were asked to refrain from exercise or caffeine consumption within 2 hours prior to their appointment, and to wear comfortable clothing and closed toed shoes (e.g., sneakers). These instructions were provided by staff making the appointment.

Informed consent process. All patients presenting to the Voice and Speech Laboratory at the MEEI with report of atypical levels of dyspnea with exertion resulting in athletic performance decrements for more than 2 weeks were approached for informed consent by the PI prior to enrollment and the start of the initial formal clinical evaluation. Informed consent was completed by participants 18 yr old and by both participants and parent/guardian for those participants under the age of 18. Information communicated during the informed consent process included the study purpose, description of the study and its procedures, potential risks and benefits, information about compensation, and procedures in the event of injury. Both the patient and the parent/guardian were given ample time to ask questions and received clarification or additional information regarding any aspect of the study as requested. Participants (age 18 yr) and participant plus parent/guardian (12-17 yr) affirmed willingness to participate by providing signatures on the Informed Consent form.

3.4 DESCRIPTION OF MANUSCRIPT CHAPTERS

The study's procedures and study findings will be addressed in the following two chapters. These chapters consist of two manuscript-ready articles for future publication. The articles were broken

down into physiological responses (Chapter 4) and perceptual responses (Chapter 5) in E-ELBD, using exercise responses in athletic volunteers as normative references. Specifically, Chapter 4 addresses glottic and supraglottic laryngeal response patterns at rest and to vigorous exercise with incremental resistance on a cycle trainer. The chapter also elucidates the role sympathovagal responses may play in E-ELBD. Chapter 5 clarifies symptoms that best represent the exercise-induced ELBD variant from a previous list of commonly ascribed symptoms: chest tightness, cough, dysphagia, globus sensation, lightheadedness, limb paresthesia, dyspnea, stridor, syncope, systemic fatigue, throat clearing, throat tightness/constriction, and dysphonia/hoarseness. Common features were identified and quantified between athletes with and without E-ELBD, and clinical diagnostic benchmarks for E-ELBD were determined. The chapter also addresses findings on temperament (stress reactivity) between the two athletic cohorts, as compared to the general adolescent population, using the EATQ-R Fear subscale. As a reminder, the term "exercise-induced paradoxical vocal fold motion disorder (E-PVFM)" was used in the two manuscripts instead of E-ELBD as this term is most familiar to medical providers and investigators studying ELBD.

4.0 MANUSCRIPT #1: PHYSIOLOGICAL FEATURES OF E-PVFM

4.1 ABSTRACT

Introduction: Exercise-induced paradoxical vocal fold motion disorder (E-PVFM) affects the lives of up to 1 million children and adolescents in the United States each year (De Guzman et al., 2014). Unfortunately, these individuals are frequently misdiagnosed due to the lack of consensus surrounding key clinical features and severity benchmarks of pathology. Consequences included missed collegiate opportunities and psychosocial consequences such as adverse effects to self-worth and personal identity, which are both crucial during the adolescent years. Therefore, the goals of this study were to (1) identify and quantify laryngeal responses indicative of E-PVFM using normative comparisons and (2) investigate the merit of the autonomic nervous system's role in E-PVFM pathogenesis for future investigations, using proxy cardiovascular estimates (i.e., systolic blood pressure and heart rate recovery).

Methods: 27 athletic teenagers were enrolled in the study. Participants with suspected E-PVFM were recruited from the Massachusetts Eye and Ear Infirmary Voice and Speech Laboratory, while healthy athletic volunteers were from the greater Boston region. Flexible laryngoscopy was conducted at rest and in conjunction with an exercise challenge. Systolic blood pressure was measured at baseline and during maximum exertion and magnitude of change for blood pressure between the two conditions was calculated. Heart rate was continuously monitored with a heart rate monitor and heart rate recovery was determined by taking the difference between heart rate (raw score) at the height of maximum exertion and two minutes post-maximum exertion. Seven naïve raters evaluated laryngeal responses using the previously recorded laryngoscopic

examinations for respective participants. Glottic responses were measured using anterior glottal angles on digital still images. The presence and severity of medial-lateral and antero-posterior supraglottic responses (arytenoid prolapse, epiglottic collapse, and ventricular compression) were determined on a 0-3 scale using previously recorded laryngoscopic videos.

Results: Glottic and supraglottic configurations were virtually identical between groups at rest. Significantly smaller glottal angles were seen in response to exercise during the inspiratory respiratory cycle in the E-PVFM group ($p = .02$) as compared to the control group ($p = .16$) during the same condition. Significantly larger expiratory glottal responses to exercise were seen in the control group ($p < .001$) but not the E-PVFM group ($p > .05$). However, there were no group differences between the E-PVFM and control groups on expiratory glottal angles at baseline ($p = .24$) or exercise ($p = .14$). Significant differences were also seen in response to exercise, compared to baseline, with arytenoid prolapse (E-PVFM: $p = .002$; control: $p = .01$) with no significant group differences seen between the groups at either the baseline or exercise conditions ($p > .05$). There were also no group or condition differences with epiglottic collapse or ventricular compression outcome parameters. Systolic blood pressure (raw) was higher in the control group than the E-PVFM group at rest and exercise. However, there were no significant differences seen between groups on magnitude of change in systolic blood pressures (ΔSBP) as a function of exercise ($p > .05$). Heart rate recovery was slightly faster in the E-ELBD group, compared to the control group. However, no significant differences in HRR were seen between the two groups.

Discussion: Inspiratory glottal adduction responses to strenuous physical activity greater than 8° may be a good diagnostic benchmark for ELBD pathology. However, further studies are needed to improve sensitivity of severity benchmarks using glottal angles as an outcome parameter. Although expiratory glottal angles with decreases more than 32° may occur in ELBD, the high

variability in laryngeal responses during the expiratory phase amongst individuals in both groups may make the parameter less sensitive. Arytenoid prolapse may be more a feature of the adolescent age group—where cartilaginous structures are more pliable and susceptible to collapse with high negative inspiratory pressures—and not necessarily a diagnostic feature of E-PVFM. Trends in higher blood pressures seen in the control group at maximum exertion and larger heart rate recovery observed in the E-PVFM group after exertion suggests further studies into the role of the autonomic nervous system in E-PVFM is warranted.

Conclusion: Study findings can increase accuracy of E-PVFM diagnosis. Results also highlight the importance of incorporating provocation challenge into the diagnosis of E-PVFM. Finally, trends in autonomic responses should be further studied to improve our understanding of underlying mechanisms driving clinical expression in E-PVFM.

4.2 INTRODUCTION

Paradoxical vocal fold motion disorder (PVFM) is an episodic breathing disorder, thought to originate from periodic paroxysmal laryngeal obstruction induced by environmental or systemic triggers (Christopher & Morris, 2010; Hoyte, 2013; Michael J. Morris & Christopher, 2010; Shembel et al., 2017). Diagnosis of PVFM has traditionally been based on patients' symptoms and "atypical" laryngeal-respiratory dynamics seen on laryngoscopic visualization. Laryngeal kinematics thought to indicate PVFM have variously been described as prolapse, narrowing, constriction, or obstruction either medially, anteroposteriorly, or both (Shembel et al., 2017). The arytenoids, aryepiglottic folds, epiglottis, ventricular folds, and/or true vocal folds have all been implicated in these patterns. However, whether any of these laryngeal features are *indicative* of

PVFM or whether they are the result of normal responses to respiratory perturbations has largely remained unexplored.

The lack of clarity in how we identify and interpret laryngeal movement in PVFM is the result of several clinical and methodological gaps. Traditionally, PVFM has been managed by healthcare providers who rarely encounter “normal” larynges in clinical settings. Without normative reference points, laryngeal configurations and kinematic patterns commonly seen in patient populations can be misinterpreted as clinical signs of pathology. For example, several studies have attributed brief bursts of partial laryngeal adduction (e.g., “twitchy larynx”) seen on endoscopy as characteristic of PVFM (Corey et al., 1998; Treole et al., 1999). However, these “twitchy” laryngeal patterns may be a normal response to something foreign (e.g., endoscope) in the laryngeal vestibule (Brancatisano, Collett, et al., 1983; England & Bartlett, 1982; Tervonen et al., 2009; Wood & Milgrom, 1996). Previous work has also suggested expiratory glottal narrowing to be a diagnostic indicator of PVFM (El-Kersh et al., 2014; Fowler et al., 2010). However, several studies have suggested glottal narrowing during expiration can occur anywhere between 10-40% in healthy individuals during the expiratory phase, depending on the larynx’s response to systemic ventilatory needs (Brancatisano, Collett, et al., 1983; Brancatisano, Dodd, et al., 1983). Finally, laryngeal dynamics evaluated in medical settings are typically assessed when the patient is asymptomatic, thus further increasing the probability of false positive findings.

To summarize, clinical biases and methodological flaws challenge current utility of laryngeal observations as reliable diagnostic indicators of PVFM. This is concerning, considering qualitative assessment of laryngeal response, typically without provocation, is the current "gold standard" approach for diagnosing PVFM. It is therefore not surprising that up to 90% of individuals are misdiagnosed, resulting in prolonged medical mismanagement (average 7.5 years)

(Bernstein, 2014; Newman et al., 1995; Traister et al., 2013). More systematic approaches, with better attention to methodology, are needed to improve diagnostic accuracy and streamline management of PVFM. Therefore, the first goal of this study was to quantify laryngeal kinematics at baseline and in response to vigorous exercise, and to compare findings between two groups: (1) patients with one type of PVFM trigger variant, exercise-induced PVFM (E-PVFM) and (2) healthy athletic adolescents without PVFM.

In addition to gaps in our understanding of laryngeal-respiratory dynamics in PVFM, there is also a poor understanding of underlying mechanisms driving these clinical presentations. Previous literature has alluded to altered balance within the autonomic nervous system (ANS) as a potential mechanism in PVFM (Ayres & Gabbott, 2002). Recent studies have also shown a positive correlation between increased intrinsic laryngeal muscle activity and heightened autonomic response with stressors in healthy subjects (Helou, 2014; Helou et al., 2013). Although currently speculative, findings suggest autonomic function could play a role in laryngeal control in the PVFM population. One way to measure autonomic response is through cardiovascular parameters. This is because the sympathetic (SNS) and parasympathetic nervous systems (PNS)—the two subsystems of the ANS—work together to regulate heart rate (HR) and heart contractibility (blood pressure). The symbiotic relationship of these subsystems is especially critical during physiological stressors, like exercise (Coote, 2010; Mador & Acevedo, 1991; Younes & Burks, 1985). During exercise, the PNS initially withdraws and the sympathetic system increases in activation, resulting in increased heart rate (Eryonucu et al., 2000). At the height of maximum exertion, the sympathetic nervous system becomes the primary responder. This response can be observed in high systolic blood pressures (SBP) and heart rates. When exercise is terminated, the right combination of sympathovagal balance is needed to return the system back to homeostatic

baseline. Parasympathetic reactivation post-maximum exertion occurs at about 44 (± 37) seconds, with sympathetic withdrawal occurring shortly after PNS reactivation (Pierpont & Voth, 2004).

Systolic blood pressure (SBP) is thought to be primarily mediated by the SNS during vigorous exertion, whereas heart rate (HR) results from sympathovagal balance in both submaximal and maximal exertion conditions (Coote, 2010; Eryonucu et al., 2000). The difference between heart rate at peak exercise and 2-minutes post-exercise—referred to as heart rate recovery—is thought to be a robust indicator of efficient sympathovagal balance (Dishman et al., 2000; Eryonucu et al., 2000; Langdeau et al., 2000; Tunnicliffe et al., 2001). HRR latency has been implicated in a variety of conditions including asthma, anxiety, and overtraining syndrome (Ayres & Gabbott, 2002; Dishman et al., 2000; Pierpont & Voth, 2004), conditions which have all been seen concomitantly with PVFM. Imbalance between the SNS and PNS (i.e., sympathovagal imbalance) could also result in aberrant exercise responses and atypical laryngeal patterns. However, whether sympathovagal balance actually plays a role in laryngeal breathing pathology has yet to be studied. Therefore, the second goal of the present study was to determine the merit of the autonomic dysfunction theory in PVFM etiology for further study.

4.3 METHODS

4.3.1 Participants

Twenty-seven adolescent athletes (13 PVFM, 14 control) were recruited for the study. Participants in the PVFM group were recruited by advertisements and referred by pediatric pulmonary and ear, nose, and throat (ENT) physicians in the Boston region. Individuals in the control group were

recruited from New England sports communities. Participants all had similar training levels (exercised 5-7 times a week, 60-120 minutes per session) and were similar in age (range = 12-18 yr). Participants were eligible for the E-PVFM group if they experienced levels of dyspnea that prevented optimal athletic performance at least once for at least 2 consecutive weeks; participants in the control group were eligible if they experienced no dyspneic symptoms detrimental to athletic performance (or exercise in general) within the past 6 months. The Dyspnea Index (DI) was administered to both groups to confirm the impact of dyspneic-related symptoms on quality of life. Patients with suspected E-PVFM were enrolled in the study if they scored more than a 10 out of 40 on the DI; healthy athletic volunteers were enrolled if they scored less than a 7 out of 40 on the DI (see *Appendix F: Dyspnea Index*[18]). For participants' safety, anyone with behavioral or cognitive deficits precluding them from following directions was excluded from the study. Participants were also excluded if they had any neurological, cardiovascular, or pulmonological disorders that could affect cardiovascular biomarker measurements or make the exercise bike challenge unsafe. Participants with asthma were excluded only if their asthma was not well controlled (not well-controlled asthma characterized as < 80% FEV1 predicted). Last, participants with intolerance to flexible endoscopy and obstructive organic lesions occluding more than a third of the upper airways were also excluded from the study.

4.3.2 Procedures

Once consented, participants were fitted with a heart rate monitor (Polar H7 Bluetooth Heart Rate Sensor & Fitness Tracker). The electrodes on the chest strap (WearLink®) were moistened with

[18] For dissertation document only.

water and the strap was placed on the chest, firmly against the skin, just below the pectoral muscles. The H7 connector was then snapped onto the strap in the center of the chest. The signal was detected using the Polar Beat app on an Android 7.1.2 cell phone. Continuous heart rate readings were automatically calculated every second throughout the entirety of the protocol. Systolic blood pressure readings and heart rate with a blood pressure cuff (Welch Allyn Spot Vital Signs LXi, Skaneateles Falls, NY) were then recorded three times consecutively while participants were trained to use a 1-8 physical exertion effort scale. A score of 1 represented no feelings of exertion, while a score of 8 represented maximum exertion that could not be sustained for longer than a minute. Participants were informed they would be encouraged to pedal until they reached an 8 on the exertion scale. A stationary trainer (SF-B1203 Indoor Cycle Trainer) was used for the exercise challenge. The height and seat of the bike was adjusted to prevent participants from gripping the handlebars, which could cause peripheral constriction and confound cardiovascular outcomes. The investigators also ensured adjustments afforded a natural flexion of the knee at maximum leg extension (10-15 degrees) while the participant was on the bike.

Once participants were seated on the trainer, oxymetazoline (Afrin®) was sprayed into the nostrils bilaterally to decongest the nasal passages. The flexible nasoendoscope (KayPENTAX EPK-1000, Kay Elemetrics Corp., Lincoln Park, NJ) was passed through the nares with the larger meatus and the laryngeal vestibule was visualized with halogen light. Structural and organic laryngeal pathology was ruled out and laryngeal movement at rest was videorecorded (*n*Stream G3, Image Stream Medical). Three consecutive blood pressure and heart rate readings were taken for the second time while participants sat still on the trainer. Laryngeal patterns at rest were observed with flexible endoscopy and simultaneously video recorded for later analysis. Two investigators monitored ribcage movement in conjunction with laryngeal response patterns

visualized on the computer monitor in real-time. Airflow from the participants' nose and mouth were also used as tactile feedback on the index finger and thumb used to stabilize the endoscope to monitor respiratory cycle bounderies. Asynchrony between laryngeal patterns and respiratory movement was addressed by verbally calling the start of each breath cycle ("I" for inspiration and "E" for expiration), as needed.

Participants were asked to pedal continuously on the trainer between 50-110 rpms while the resistance on the trainer was incrementally increased one lever rotation every 30 seconds, determined by a stopwatch. The goal was to ramp up resistance on the bike while participants pedaled as hard as they could without so much resistance as to prevent participants from being able to pedal. Laryngeal-pulmonary synchronization was monitored simultaneously with the exercise challenge using the same methods as for the baseline laryngoscopy condition. Additionally, a lapel microphone (KayPENTAX EPK-1000, Kay Elemetrics Corp., Lincoln Park, NJ), placed in front of the participants to capture audible breaths and calling of the breath cycles when needed, was used to later confirm respiratory cycle boundaries for data extraction. Participants in the control group pedaled on the trainer until they reported an 8 on the exertion scale, at which point an additional 30 seconds of videoendoscopy was recorded prior to the exercise protocol being terminated. Participants in the experimental group cycled with 30-second incremental resistance loads until an 8 was reported on the exertion scale or a PVFM dyspneic episode was provoked, at which point 30 additional seconds of laryngeal movement was recorded before the exercise challenge was terminated. Participants were also asked to stop pedaling at the 3-minute mark if symptoms were not elicited at an exertion level of 8 in the experimental group. At the point of maximum exertion (8 on the scale), or in the case of a PVFM attack, three consecutive readings of systolic blood pressure and heart rate were taken for the third and final

time. The heart rate monitor was kept on the chest until the heart rate reached baseline readings, before being removed, to capture heart rate recovery readings and to ensure safety of participants. Raw heart rate readings were also compared between groups (see Table 4-1 for summary of experimental protocol stages and Figure 4-1 for example of exercise laryngoscopy setup, respectively).

Table 4-1. Experimental Protocol Stages

Stage I: Screening	Stage II: Pre-Baseline	Stage III: Baseline Laryngoscopy	Stage IV: Exercise Laryngoscopy
IA. Case History	IIA. Heart rate monitor fitted and app started	IIIA. Laryngoscopy (at rest)	IVA. Continuous Exercise Laryngoscopy w/ cycle trainer)
IB. Dyspnea Index	IIB. SBP and HRR Recordings - 1	IIIB. SBP Recordings - 2	IVB. SBP Recordings - 3
	IIC. 1-8 Physical Effort Scale Training		
	IID. Trainer adjustment		
	IIE. Oxymetazoline administration		

Figure 4-1. Cycle trainer exercise challenge setup

4.3.2.1 Glottal angle and supraglottic response patterns

For each participant, two 30-second videos of previously recorded laryngeal breathing patterns, sans phonation or swallow response, were created, first for the baseline (rest) laryngoscopy condition and second for the maximum exertion (exercise) condition. Videos were extracted into two distinct MP4 files for the two respective conditions for a total of 54 videos. These videos were later used to rate supraglottic responses. Eight digital still images of laryngeal configuration from each participant's laryngeal examination (216 total) were also extracted, with two sets taken during each of the following conditions: (1) height of inspiration at baseline rest, (2) height of expiration at baseline rest, (3) height of inspiration during maximum exertion (or PVFM attack), and (4) height of expiration during maximum exertion (or PVFM attack). Boundaries of respiratory cycles were determined by investigator verbal feedback ("I" and "E") or audible breaths with the

microphone simultaneously recorded previously on the laryngoscopy videos. Thirty percent (30%) of the 54 videos and 30% of the 216 digital stills were each randomized separately for each of the seven independent raters so that each of the videos and images were analyzed at least twice.

To analyze the digital stills, the seven raters (range: 3-20 years of laryngoscopic assessment experience) blinded to group and condition, were asked to manually identify anterior glottal angles of their respective analyzed images using a computer mouse and customized MATLAB program (see McKenna, Murray, Lien, & Stepp, 2016 for details). Raters were fellowship trained laryngologists or clinically certified voice-specialized speech-language pathologists who all had at least three years of experience with laryngoscopic examinations. In short, raters were asked to first identify the medial edge of each vocal fold. Raters then placed a coordinate at the medial tip of the right vocal process with a single click of the mouse, followed by double clicking the mouse at the vertex of the anterior commissure on the ipsilateral side (or slightly past the commissure) to create a line that followed the medial edge of the superior vocal fold. The same patterns were conducted on the left vocal fold, creating crosshairs at the anterior commissure (Figure 4-2). Anterior glottal angles were calculated from the crosshairs and automatically populated into an Excel spreadsheet using the customized MATLAB program.

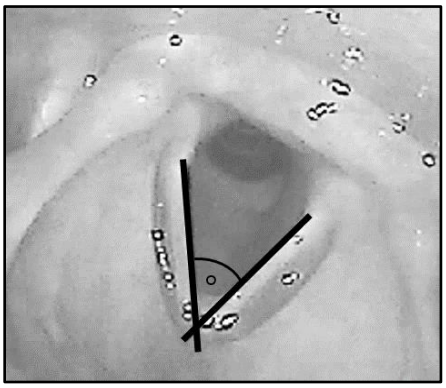


Figure 4-2. Anterior glottal angle measurements.

For images where the glottis could not be visualized due to arytenoid obstruction, raters were instructed to place coordinates anterior of the vocal process and follow the marginal edges of the superior vocal fold to (or slightly past) the anterior commissure. Raters were then asked to mark the image with the letters "PO" (for posterior obstruction)[19] (Figure 4-3(A)). If the anterior commissure was occluded (e.g., epiglottic collapse), raters were asked to start at the vocal process posteriorly and follow the marginal edges of the superior true vocal folds until crosshairs were created anteriorly. Raters were then asked to mark the image with the letters "AO" (for anterior obstruction)[20] (Figure 4-3(B)). Raters then commented whether they thought the obstruction was due to camera angle or as a result of supraglottic movement. Once all raters had analyzed the images, intraclass correlation coefficients (ICC) for each respective image were calculated, and once robust ICCs were confirmed (see Section 4.4.2 for details), the angles for each image were averaged across the seven raters.

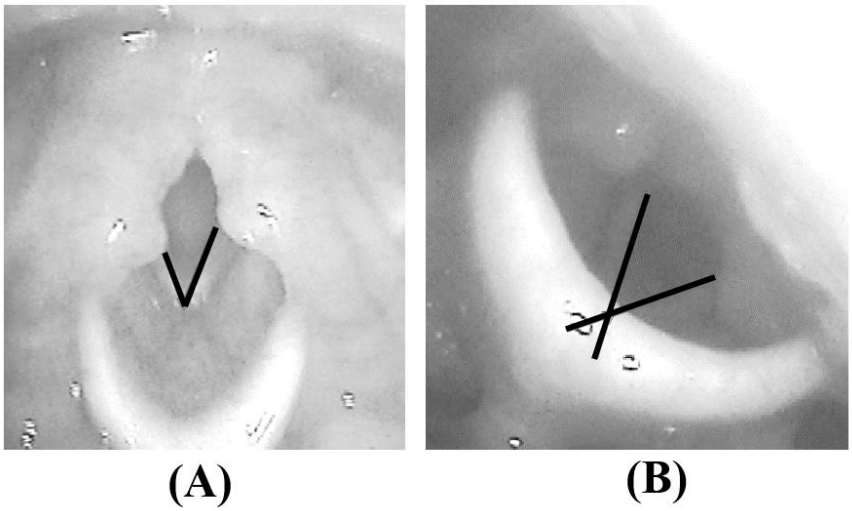


Figure 4-3. (A) Example of anterior glottal angle acquisition for images with posterior glottal obstruction (e.g., arytenoids). (B) Example of anterior angle acquisition for images with anterior obstruction (e.g., epiglottis).

[19] Reported in 8% of images
[20] Reported in 11% of images

The same raters then rated the severity of supraglottic obstruction (arytenoid prolapse, epiglottic collapse, and ventricular compression) on pre-recorded laryngoscopy videos for both baseline and exercise conditions, using a 0-3 severity scale (Table 4-2). The audio track for all the videos was muted so as not to bias raters to the condition (rest versus exercise) which could affect their rating responses. Ratings were documented on an Excel spreadsheet. Raters were also asked to document any other atypical laryngeal presentations they saw (e.g., edema, quivering arytenoids) and to indicate poor images that could affect accuracy of laryngeal analysis, using the same spreadsheet. Once ratings had been conducted for all seven raters. severity ratings for each video were averaged to the nearest integer across the seven raters for each video.

Table 4-2. Rating System for Supraglottic Laryngeal Responses

Obstruction Type	0	1	2	3
Arytenoid prolapse[1]	Expected maximal abduction of the aryepiglottic folds with no visible medial rotation (top of cuneiform tubercles pointed vertical or slightly lateral)	Visual medial rotation of the cranial edge of the aryepiglottic folds and tops of the cuneiform tubercles	Further medial rotation of the cuneiform tubercles with exposure of the mucosa on the lateral sides of the tubercles	Medial rotation until near horizontal position of the cuneiform tubercles and tops of the cuneiform tubercles move towards the midline
Epiglottic Collapse[2]	Epiglottis hugs the tongue	Epiglottis between 0-45°	Epiglottis between 45-90°	Epiglottis over 90°
Ventricular (False) Fold compression[3]	Absent	1/3 of the true vocal folds covered	2/3 of the true vocal folds covered	True vocal folds completely hidden

[1]Validated by Maat (2011); [2]validated by Catalfumo et al., (1998); [3]validated by Schonweile et al (1998)

4.3.2.2 Autonomic biomarkers

Systolic blood pressure readings acquired at pre-baseline and baseline laryngoscopy were each averaged across the three readings for each respective condition. Readings across the three timepoints, pre-baseline (ave. x3), baseline laryngoscopy (ave. x3), and maximum exercise laryngoscopy (x1) were compared between groups. The magnitude of change in systolic blood pressure from pre-baseline (rest) to maximum exertion (exercise challenge) was then calculated for each participant. Heart rate raw scores acquired from the blood pressure cuff and heart rate monitor were compared to confirm robust reliability. Scores were also used to determine whether there were differences between groups across the conditions. Heart rate recovery was then calculated using the raw heart rate scores. The highest heart rate reading acquired at maximum exertion was subtracted from the heart rate reading acquired two minutes after the maximum exertion timepoint.

4.3.2.3 Statistical analysis

Intraclass correlation coefficients (two-way mixed model, absolute agreement) were run for glottal angles (inspiration and expiration) across the seven raters to determine absolute interrater reliability. A series of nonparametric statistical tests (Kruskal Wallis H test, Mann-Whitney U test, Wilcoxon Sign-Rank test) were conducted to determine group (E-PVFM, control) and condition (rest, exercise challenge) differences for glottal angles and supraglottic responses. For the autonomic parameters, factorial Analysis of variances (ANOVAs) were conducted on raw systolic blood pressure and heart rate readings. Independent samples *t* tests were performed between groups as a function of condition, with magnitude of systolic blood pressure response and heart rate recovery as the dependent variables, respectively. All parametric and nonparametric statistical analyses were corrected with Bonferroni adjustment to account for Type 1 errors.

4.4 RESULTS

4.4.1 Demographics

There were 9 females and 4 males in the E-PVFM group and 9 females and 5 males in the control group. One participant (male) of the 13 total participants in the E-PVFM group was not induced with provocation challenge and the laryngeal data for that participant were removed from analysis. Mean age of participants analyzed was 14.33 years (SD = 1.97) for the PVFM group and 16.87 (SD = 1.19) for the control group. Participants were all competitive athletes and engaged in at least one organized, aerobic sport/athletic activity per year. The average length of time it took to reach maximum perceived exertion during the exercise challenge protocol in the present study was around 5 minutes in both E-PVFM and control groups (277.00 ±85.87 sec. and 265.71 ±48.48 sec., respectively).

4.4.2 Reliability Measures: Glottal Angles

Interrater reliability for glottal angle (inspiration and expiration) was statistically robust across the seven raters for both baseline and exercise laryngoscopy conditions (Table 4-3). The average intraclass correlation coefficient (ICC) was 0.95 (*SD* = 0.05), with a range of 0.75-0.995. These findings corresponded with previous work by McKenna and colleagues (2016) that showed intraclass correlation coefficients to be 0.91 for laryngeal kinematic calculations using the same laryngeal landmark identification protocol. Strong correlations across raters, despite the varying levels of clinician experience, confirm the utility of glottal angle measurements in both clinical and academic settings.

Table 4-3. Interrater Reliability for Glottal Angle

	Rater 1	Rater 2	Rater 3	Rater 4	Rater 5	Rater 6	Rater 7
Rater 1		0.973	0.968	0.977	0.981	0.962	0.983
Rater 2			0.957	0.901	0.995	0.936	0.986
Rater 3				0.747	0.952	0.987	0.983
Rater 4					0.983	0.882	0.969
Rater 5						0.964	0.989
Rater 6							0.918
Rater 7							

4.4.3 Glottal Angle (inspiration)

Descriptively, anterior glottal angles at the height of inspiration were highly similar at baseline laryngoscopy (rest) between the E-PVFM (M = 53.33°, SD = 10.36°) and control (M = 52.69°, SD = 8.17°) groups (d = 0.07). However, inspiratory glottal angles during exercise were smaller in the E-PVFM group (M = 44.75°, SD = 17.81°), compared to the control group (M = 54.31°, SD = 7.57°) (d = 0.70) (Figure 4-4). Statistically, data for inspiratory glottal angle violated assumptions of normality and variance. Therefore, a series of nonparametric tests were conducted. Kruskal-Wallis H tests showed group differences between glottal angles (raw) with inspiration were not significant at baseline (p = .24) or exercise (p = .19), likely due to variable glottal angle differences across participants. However, results did show *magnitude* of change, from baseline to exercise, was significantly smaller in the E-PVFM group (p = .04) than the control group, as assessed by a Mann-Whitney U test. Wilcoxon Signed-Rank tests also revealed a significant effect of exertion in the E-PVFM group (p = .02) but not in the control group (p = .16).

4.4.4 Glottal Angle (expiration)

On average, glottal angles measured at the height of expiration were also highly similar between the E-PVFM and control groups at rest (M = 36.33°, SD = 11.08°; M = 36.35°, SD = 9.20°, respectively; d = 0.002). However, during the exercise challenge, expiratory glottal angles were slightly larger in the control group (M = 49.20°, SD = 9.95°) as compared to the E-PVFM group (M = 40.25°, SD = 16.66°) (d = 0.65) (Figure 4-4). Statistically, the data violated assumptions of normality and variances and a series of nonparametric tests were therefore conducted. The Kruskal-Wallis H test showed no statistically significant differences in glottal angle (raw) between groups at baseline (p = .85) or exercise (p = .14). The Mann-Whitney U test also showed no statistically significant differences in magnitude of change in glottal angle at the height of expiration from baseline to exercise laryngoscopy conditions across the two groups (p = 0.06). However, Wilcoxon Signed-Rank tests did show a significant increase in glottal angles with expiration during maximum exertion from rest in the control group (p < .001), but not the E-PVFM group (p > .05).

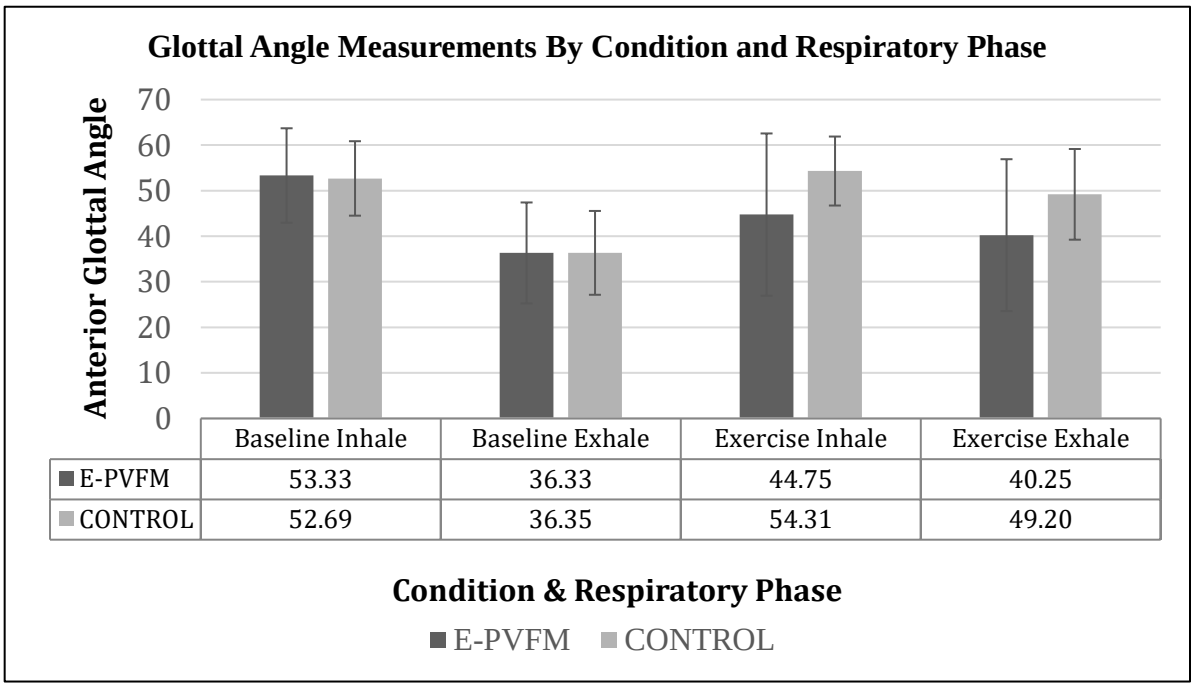


Figure 4-4. glottal angle (inspire and expire) configuration

4.4.5 Supraglottic Laryngeal Responses

4.4.5.1 Arytenoid movement

Descriptively, 25% of participants in the PFVM group and 21% in the control group were rated by the raters as having mild medial arytenoid movement (1 on 0-3 scale) at rest (baseline laryngoscopy). During exercise, 92% of participants in the E-PVFM group and 79% in the control group showed some level of medial arytenoid activity (rating of 1 or more on 0-3 scale), with 50% in the E-PVFM group and 25% in the control group exhibiting moderate medial arytenoid prolapse (2 on 0-3 scale). No participants in either group were rated as having severe arytenoid prolapse (3 on 0-3 scale) (Table 4-4). Statistically, there were no significant differences between groups on amount of arytenoid activity at baseline (p = 0.83) or exercise (p = 0.22) laryngoscopy, as assessed by a Kruskal-Wallis H Test. Wilcoxon Signed-Rank tests showed exercise had a significant effect

on arytenoid response in both the E-PVFM group (p = .002) and control group (p = .01) (Figure 4-5Figure 4-5. Supraglottic Laryngeal Responses).

4.4.5.2 Epiglottic collapse

Descriptively, 33% of participants in the E-PVFM group and 14% in the control group were rated as having mild epiglottic movement (between 0-45 degrees towards the level of the glottis) at rest (1 on 0-3 scale). One individual in the control group was rated as having moderate epiglottic movement (2 on 0-3 scale). During exercise, 17% of participants in the E-PVFM and 21% in the control group were rated as having mild collapse towards the level of the glottis, with no participants exhibiting moderate (2 out of 3) or severe (3 out of 3) epiglottic movement during exercise (Table 4-4). There were no statistically significant differences between groups on amount of epiglottic activity at baseline (p = 0.33) or exercise (p = 0.76) laryngoscopy, as assessed by a Kruskal-Wallis H Test. Wilcoxon Signed-Rank tests also showed there were no significant epiglottic responses to exercise in either the E-PVFM group (p = .32) or control group (p = 1.00) (Figure 4-5).

4.4.5.3 Ventricular (false fold) compression

Ventricular compression was not seen at rest in either the E-PVFM or control groups. During maximum exertion, raters identified mild ventricular compression in 17% of participants in the E-PVFM group and 21% in the control group (Table 4-4). There were no statistically significant differences between groups on amount of false fold activity at baseline (p = 1.00) or exercise (p = 0.76) laryngoscopy, as assessed by a Kruskal-Wallis H Test. Exercise did not have a significant effect on ventricular medial response in either the E-PVFM group (p = .56) or control group (p = .05), as assessed by Wilcoxon Signed-Rank tests (Figure 4-5).

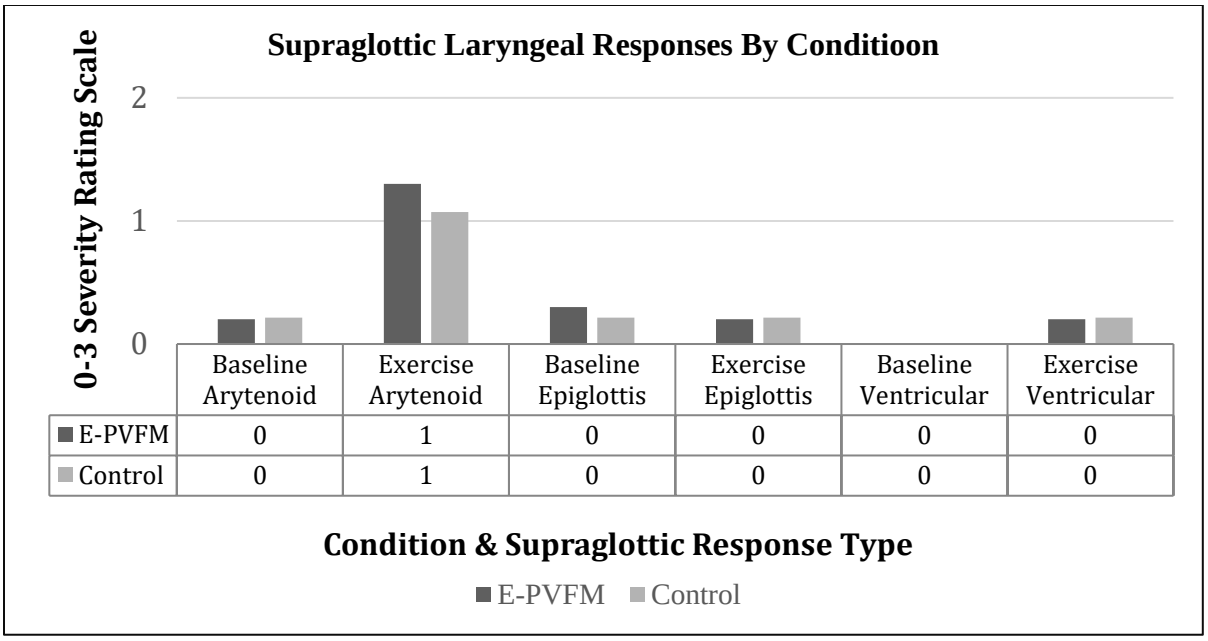


Figure 4-5. Supraglottic Laryngeal Responses

Table 4-4. Descriptive Findings for Supraglottic Patterns at Baseline (Rest) and Maximum Exertion (Exercise Challenge) in participants with E-PVFM and Controls. Prevalence is based the 0-3 severity rating scale

Supraglottic Patterns		**E-PVFM**			**Control**		
Arytenoid Prolapse	Baseline	0: 75%	1: 25%	2: 0%	0: 79%	1: 21%	2: 0%
	Exercise	0: 8%	>1: 92%	2: 50%	0: 21%	>1: 79%	2: 25%
Epiglottis Collapse	Baseline	0: 67%	1: 33%	2: 0%	0: 78%	1: 14%	2: 7%
	Exercise	0: 83%	1: 17%	2: 0%	0: 79%	1: 21%	2: 0%
Ventric. Compres.	Baseline	0: 100%	1: 0%	2: 0%	0: 100%	1: 0%	2: 0%
	Exercise	0: 83%	1: 17%	2: 0%	0: 79%	1: 21%	2: 0%

4.4.6 Sympathovagal Balance Biomarkers

4.4.6.1 Systolic blood pressure

Descriptively, systolic blood pressure readings at rest and during rigorous exercise were higher in the control group than the E-PVFM group (Figure 4-6). A mixed-design factorial ANOVA was

conducted to determine whether there were statistically significant differences in systolic blood pressure readings over the three conditions: pre-baseline, baseline laryngoscopy, and exercise laryngoscopy between the E-PVFM and control groups. There were no outliers in the data, characterized as studentized residual values greater than +/-3. The assumption for normality was met, as assessed by Shapiro-Wilk's test of normality ($p > .05$). Homogeneity of variance was met for all three conditions (pre-baseline, baseline, and exercise) ($p > .05$), as assessed by Levene's test of homogeneity of variances. Homogeneity of covariances was met ($p > .05$), as assessed by Box's M test. Mauchly's test of sphericity indicated that the assumption of sphericity was violated for the two-way interaction, $\chi 2(2) = 14.430$, $p < .001$. Epsilon (ε) was .661, as calculated according to Greenhouse & Geisser (1959), and was used to correct the mixed-design factorial ANOVA. There was no statistically significant interaction between group and condition on systolic blood pressure, $F(1.321, 27.742) = .215$, $p = .714$, partial $\eta 2 = .010$. The main effect of condition showed a statistically significant difference in mean systolic blood pressure measures at the three different time points, $F(1.321, 27.742) = 77.465$, $p < .001$, partial $\eta 2 = .787$. The main effect of group showed significantly higher systolic blood pressure measurements in the control group (M = 130.03 mmHg, SE = 2.62 mmHg) as compared to the E-PVFM group (M = 118.40 mmHg, SE = 2.85 mmHg) $F(1, 21) = 7.726$, $p = .011$, partial $\eta 2 = .269$. Post hoc analysis with a Bonferroni adjustment revealed that systolic blood pressure measurements were statistically higher in the exercise condition (M = 143.98, SE = 3.06) than the pre-baseline (M = 113.50 mmHg, SE = 1.78 mmHg) and baseline (M = 115.16 mmHg, SE = 2.44 mmHg) conditions, respectively ($p < .001$). There were no significant differences between the pre-baseline and baseline conditions ($p = .635$) (see Table 4-5 for SBP descriptive statistics and Figure 4-6 for visual representation of SBP for the two groups across the three conditions and post-maximum exertion. Raw systolic blood

pressure readings at the 2- and 3-minute post-maximum exertion time points have also been included for comparison).

Table 4-5. Descriptive Statistics for Raw Systolic Blood Pressure Readings Across Conditions

Descriptive Statistics for Systolic Blood Pressure Readings					
	Group	**Mean (mmHg)**	**Std. Dev. (mmHg)**	**N**	**Cohen's *d***
Pre-Baseline	E-PVFM	108.17	7.39	11	1.24
	Control	118.83	9.60	13	
	Total	113.94	10.07	24	
Baseline Laryngoscopy	E-PVFM	109.76	13.16	11	0.90
	Control	120.56	10.73	13	
	Total	115.61	12.87	24	
Exercise Laryngoscopy	E-PVFM	137.27	17.16	11	0.89
	Control	150.69	12.78	13	
	Total	144.54	16.12	24	
2 Minutes Post-Max Exertion	E-PVFM	130.70	17.77	10	1.02
	Control	147.76	15.54	13	
	Total	140.35	18.32	23	
3 Minutes Post-Max Exertion	E-PVFM	128.00	21.30	5	0.57
	Control	137.83	11.81	6	
	Total	133.36	16.66	11	

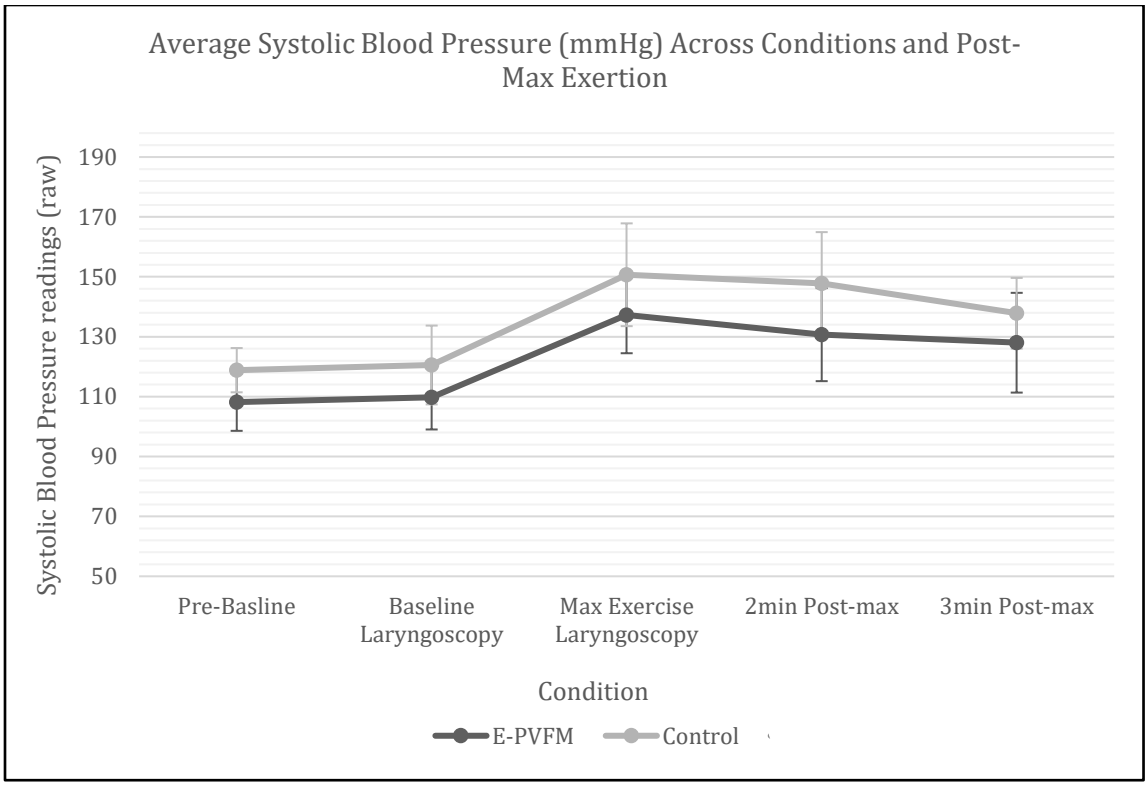


Figure 4-6. Means and standard deviations for systolic blood pressure across conditions.

An independent samples *t* test was conducted to determine whether there were group differences in magnitude of sympathetic response to exercise—as measured via systolic blood pressure changes from baseline to exercise (ΔSBP)—between E-PVFM and control groups. There were no outliers in the data, as assessed by boxplot. Systolic blood pressure readings were normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$) and assumption of homogeneity was met, as assessed by Levene's test for equality of variances ($p = .47$). ΔSBP (measured in mm Hg) was greater in the control group ($M = 31.86$ mmHg, $SD = 11.12$ mmHg) than the E-PVFM group ($M = 29.11$ mmHg, $SD = 16.00$ mmHg). However, there was no statistically significant difference between the two groups, $t(22) = -0.50$, $p = .63$, $d = 0.20$.

4.4.6.2 Heart rate recovery

Descriptively, heart rate (bpm) at rest (pre-baseline and baseline laryngoscopy) and maximum vigorous exercise were highly similar between groups (Figure 4-7). A mixed-design factorial ANOVA was conducted to determine whether there were statistically significant differences in raw heart rate readings across the three conditions: pre-baseline, baseline laryngoscopy, and exercise laryngoscopy between the E-PVFM and control groups. There were no outliers in the data, characterized as studentized residual values greater than +/-3. The assumption for normality was met, as assessed by Shapiro-Wilk's test of normality ($p > .05$). Homogeneity of variance was met for pre-baseline and exercise conditions ($p > .05$), but not for baseline laryngoscopy condition ($p = .004$), as assessed by Levene's test of homogeneity of variances. Homogeneity of covariances was violated ($p = .003$), as assessed by Box's M test. Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi2(2) = 1.07$, $p = .59$. There was no statistically significant interaction between group and condition on heart rate, $F(2, 50) = 1.48$, $p = .24$, partial $\eta2 = .056$. The main effect of condition showed a statistically significant difference in mean heart rate measures at the different time points, $F(2, 50) = 558.20$, $p < .001$, partial $\eta2 = .957$. There were no significant differences in group for heart rate measures $F(1, 25) = 0.003$, $p = .96$, partial $\eta2 = .000$. Post hoc analysis with a Bonferroni adjustment revealed that heart rate measures were statistically higher in the exercise condition ($M = 167.06$ bpm, $SE = 2.08$ bpm) than the pre-baseline ($M = 79.34$ bpm, $SE = 2.80$ bpm) and baseline ($M = 85.20$ bpm, $SE = 3.20$ bpm) conditions, respectively ($p < .001$). There were no significant differences between the pre-baseline and baseline conditions ($p = .11$). (see Table 4-6 for HR descriptive statistics and Figure 4-7 for visual representation of raw HR readings for the two groups across the three conditions and post-

maximum exertion. Raw heart rate readings at the 1-, 3-, and 20-minute minute post-maximum exertion time points have also been included for comparison).

Table 4-6. Descriptive Statistics for Raw Heart Rate Readings (in bpm) Across Conditions

Descriptive Statistics for Heart Rate (Raw Readings)					
	Group	**Mean (bpm)**	**Std. Dev. (bpm)**	**N**	**Cohen's *d***
Pre-Baseline	E-PVFM	76.54	14.84	13	0.38
	Control	82.13	14.29	14	
	Total	79.44	14.56	27	
Baseline Laryngoscopy	E-PVFM	86.64	21.41	13	0.17
	Control	83.76	10.42	14	
	Total	85.15	16.37	27	
Exercise Laryngoscopy (Max Exertion)	E-PVFM	168.77	8.58	13	0.32
	Control	165.36	12.52	14	
	Total	167.00	10.75	27	
1min Post-max Exertion	E-PVFM	132.38	21.60	13	0.05
	Control	131.31	20.93	14	
	Total	132.37	20.84	27	
2min Post-max Exertion	E-PVFM	114.69	19.61	13	0.05
	Control	115.69	18.24	14	
	Total	115.89	18.58	27	
3min Post-max Exertion	E-PVFM	113.85	20.83	13	0.11
	Control	111.69	17.06	14	
	Total	112.93	18.62	27	
20min Post-max Exertion	E-PVFM	95.00	19.42	13	0.33
	Control	101.23	17.37	14	
	Total	98.41	18.34	27	

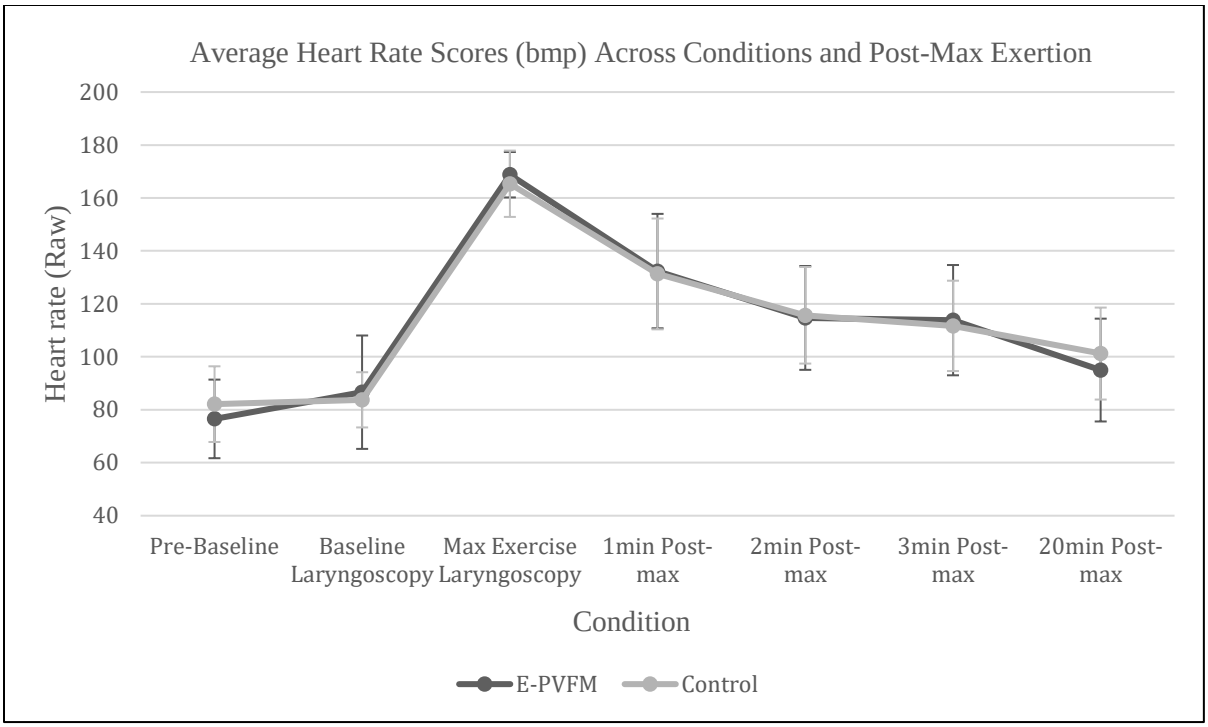


Figure 4-7. Means and standard deviations for heart rate (raw readings) across conditions (pre-baseline, baseline, and exercise)

An independent samples *t* test was also conducted on 2-minute post-exertion heart rate recovery (2-min HRR) to determine whether there were group differences in parasympathetic reactivation after maximum exertion between the two groups. There were no outliers in the data, as assessed by boxplot. The assumption of normality was met, as assessed by Shapiro-Wilk's test of normality ($p > .05$). Homogeneity of variance was also met ($p > .05$), as assessed by Levene's test of homogeneity of variances. Two-minute HRR was greater in the E-PVFM group ($M = 54.08$, $SD = 15.10$) than the control group ($M = 49.15$, $SD = 15.91$). However, differences between the two groups were not statistically significant, $t(24) = 0.81$, $p = .43$, $d = 0.32$.

4.5 DISCUSSION

During quiet respiration, glottal configurations between the groups were almost identical. Both groups showed phasic glottal widening during inspiration and glottal narrowing during expiration. On average, glottal angles decreased from inspiration to expiration by 32%. Findings of laryngeal patterns at rest (without provocation) in both E-PVFM and control groups are consistent with those from previous literature which show the glottis decreases from inspiration to expiration during vegetative breathing in healthy controls anywhere between 10-40% (Brancatisano, Collett, et al., 1983). Laryngeal response patterns to exercise in the control group were also similar to those reported in previous studies. From baseline (rest) to maximum exertion (exercise challenge), the control group's glottal angles increased with both inspiration (average increase: 2%) and expiration (average increase: 36%). These laryngeal patterns are thought to augment airway patency in order to meet greater ventilatory demands with exercise (Brancatisano, Dodd, et al., 1983), especially during expiration.

Conversely, in the E-PVFM group, glottal angles *decreased* with exercise (from rest) during inspiration (average decrease: 15%), with statistically significant differences between groups observed during the same condition. Nine out of 13 participants had more than an 8° decrease in anterior glottal angle with exercise during inspiration. These patterns align with previously documented inspiratory "paradoxical" findings described in the literature (e.g., Beaty, Wilson, & Smith, 1999), and are thought to be counterproductive for meeting high ventilatory demands during strenuous exercise.

With expiratory glottal angles in the E-PVFM group, the angles also increased in response to exercise (from rest). However, unlike in the control group, laryngeal responses were not significantly different between rest and exercise. In fact, these responses showed to be more

blunted in the E-PVFM group (average increase: 11%) during exercise as compared to the control group (average increase: 36%) in the same condition. Expiratory findings could point to a reduction in respiratory efficiency in patients with E-PVFM, as opposed to frank "paradox" (seen with inspiration). Interestingly, while the majority of participants in the E-PVFM group had abducted vocal fold responses to exercise (albeit blunted), two out of the thirteen participants in the same group did have adductory responses to exertion with expiration (3-4° and 15-20° expiratory glottal angle decreases with exercise from baseline, respectively). These findings show that there may be some variability in response patterns with the expiratory cycle in patients with E-PVFM and point to potential differences in mechanisms underlying these glottal response patterns. Findings may also point to a disordered respiratory and laryngeal system that may manifest in disturbed or discoordinated physiological patterns that differ from patient to patient with potentially similar underlying mechanism(s).

Overall, results showed decreased inspiratory glottal configurations, characterized by paradoxical vocal fold adduction, is a good diagnostic indicator of E-PVFM. Blunted abducted (and in some cases paradoxical adducted) expiratory laryngeal patterns may also be observed in response to exercise in patients with E-PVFM. However, because these patterns were not significantly different from athletic controls they may not be as robust a clinical indicator of E-PVFM. Additionally, the fact that these pattern differences were only present during exercise highlights the need to implement provocation challenges into clinical practice to prevent over- or under-diagnosis of PVFM.

Supraglottic patterns showed higher prevalence of medial arytenoid movement patterns during exercise (compared to rest) in both groups. Although the prevalence of arytenoid prolapse was slightly higher in the E-PVFM group (compared to control) during exercise, there were no

significant differences between the two groups ($p > 0.05$) at rest or exercise. These results suggest arytenoid response patterns may occur variably in young athletes in general, and the presence of these patterns may not necessarily be *indicative* of E-PVFM, although future investigation with larger cohorts are needed to be sure. Prolapsed arytenoids are thought to occur with substantial negative inspiratory pressures (i.e., Bernoulli effect, Venturi effect) or alterations in muscle tone, causing laryngeal tissues to draw together (Bent et al., 1996; Christopher & Morris, 2010). These significant pressure changes may occur during maximum exertion or strenuous physical activity, which could explain why supraglottic obstruction might be more prevalent in athletes (Christopher & Morris, 2010; Nagai et al., 1992; Pinho, Tsuji, Sennes, & Menezes, 1997). The smaller diameter of the airways in younger individuals, which can create more negative pressure, combined with increased pliability of the larynx in the pediatric population (Hudgins, Siegel, Jacobs, & Abramowsky, 1997), could explain the higher prevalence of medial movement of the arytenoids seen in young athletes during high physical demands.

Additionally, the lower prevalence of epiglottic and ventricular responses in both groups across conditions may suggest these patterns could be more representative of other PVFM variants (e.g., Irritable Larynx Syndrome) than of the exercise PVFM variant. The supraglottic patterns found in this study align with previous work. In a study by Christensen and colleagues, paradoxical glottal movement of the true vocal folds, as well as supraglottic prolapse of the arytenoids, were noted during a continuous laryngoscopy exercise (CLE) test in the majority of 97 adolescent athletes diagnosed with E-PVFM (Christensen et al., 2010). Abu-Hasan and colleagues (2005) also found paradoxical glottal movement, as well as arytenoid and epiglottal prolapse, but the latter presentation only occurred in 13 out of 142 participants with exercise-induced dyspnea during a similar exercise task.

Interestingly, when raters were asked to freely note any additional laryngeal features they thought indicated E-PVFM, five out of the seven raters reported presence of "twitchy" larynges and edema/erythema. When blinded to group and condition, prevalence of "twitchiness" identified by the raters was slightly higher in the control group (29% [4/14]) than the E-PVFM group (17% [2/12]). The presence of edema/erythema was similar between the E-PVFM group (17% [2/12]) and control group (14% [2/14]). These findings point to the need for caution when extrapolating laryngeal findings to PVFM pathology in absence of normative reference points. However, further investigation is needed to determine the role of these physiological responses in PVFM across larger sample sizes, different trigger variants (e.g., irritant-induced), and different pathological cohorts with similar signs and symptoms to E-PVFM (e.g., exercise-induced asthma, anxiety disorders).

There were no *statistically* significant differences between groups on sympathovagal responses to exercise. However, lower SNS trends seen in the E-PVFM group, in spite of seemingly alarming PVFM subjective "attacks," when combined with slightly faster PNS reactivation post-exertion, may point to autonomic dysfunction as a potential mechanism in *some* individuals with E-PVFM. These findings align with previous studies showing PNS hyperfunction and SNS hypofunction in patients with asthma, reflux disorders, and chronic vasomotor rhinitis (Ishman et al., 2007; Jaradeh et al., 2000; Loehrl et al., 2002). Interestingly, these conditions have high comorbidities with PVFM. Studies by Helou and colleagues also showed increased parasympathetic responses to high physiological (cold pressor task) and psychological (public speaking task) demands placed on the body—with simultaneous increases in intrinsic laryngeal muscle activity—in two cohorts of healthy individuals, compared to biomarker parameters at

homeostatic baseline (Helou, 2014; Helou et al., 2013). Findings of the present study warrant future investigations into the role(s) sympathovagal balance plays in PVFM.

Interestingly, exercise—a different type of physiological stressor than the one used by Helou and colleagues—perturbs respiratory patterns (volume, flow, and timing), causing changes in ventilatory responses. The ANS typically alters these perturbed respiratory patterns to accommodate increased respiratory demands placed on the system with exercise. However, with *chronic* demands placed on the system, the sympathetic and parasympathetic systems can become imbalanced (Brame & Singer, 2010). Too much parasympathetic activity could result in vagally-mediated tension within the intrinsic laryngeal muscle adductors or reduced laryngeal tone in the abductor muscles, reducing airway patency (Streeter, Gerbarg, Saper, Ciraulo, & Brown, 2012). Although the theory is at this point speculative, it could help explain laryngeal patterns found within the E-PVFM cohort, and can facilitate direction of future investigations.

It is important to note that it is not suggested that the ANS *does* play a role in E-PVFM but that it *could* play a role. Due to the high variability in autonomic responses amongst participants, combined with the small sample size in the present study, caution should be taken so as not to over-attribute ANS dysfunction to PVFM. Further investigations with larger, appropriately powered sample sizes are needed to further confirm or refute this theory. Specifically, an interim power analysis suggests that 788 participants (394 E-PVFM and 394 healthy controls) would need to be recruited to provide 80% statistical power to detect a clinically significant difference between magnitude of change in systolic blood pressures using independent t tests with an alpha level of 0.05 (Cohen's $d = 0.2$). For the 2-minute heart rate recovery parameter, 352 total participants (176 E-PVFM and 176 healthy controls) would need to be recruited to provide 80% statistical power to detect a clinically significant difference between magnitude of change in systolic blood pressures

using independent t tests with an alpha level of 0.05 (Cohen's d = 0.3). However, preliminary findings showing trends in lower systolic blood pressure responses to exercise, combined with faster heart rate recovery post-exercise in the E-PVFM group in many of the participants is curious and should be further explored.

There were several limitations to the study surrounding the blood pressure readings that should be noted. First, average systolic blood pressures were higher in the control group than the E-PVFM group across conditions. Findings were primarily attributed to trends in autonomic dysregulation in the experimental group. However, the lower blood pressures seen in the E-PVFM group at rest and with laryngoscopy (baseline and exercise) could instead have been attributed to the extra 15-20 minutes participants in the E-PVFM group remained seated after they were consented and completed the screening form but prior to the start of the protocol. During this time patients with suspected E-PVFM were given brief psychoeducational counseling on PVFM principles. However, both groups remained seated for at least half an hour after they arrived at the Voice and Speech Laboratory at the Massachusetts Eye and Ear Infirmary while they underwent the consent process, screening, and completed the Dyspnea Index. Previous studies suggest the amount of time the participants sat prior to starting the protocol (~30 minutes) was sufficient for cardiovascular parameters to reach homeostatic baseline (Al Haddad, Laursen, Chollet, Ahmaidi, & Buchheit, 2011; Becker, Silva, Moreira, & Victor, 2007; Buchheit et al., 2008; Muntner P, He J, Cutler JA, Wildman, & Whelton, 2004; Singh, Rhodes, & Gauvreau, 2008). Regardless, future studies should incorporate psychoeducational counseling for both groups into the study's protocol to keep the design of the study as consistent as possible.

Second, blood pressure readings during maximum exertion needed to be initiated immediately at the point of exercise cessation due to the sensitivity of the blood pressure cuff to

physical movement. Therefore, acquisition of SBP for the maximum exertion readings took an additional 10-20 seconds after the participant stopped pedaling on the trainer to account for inflation and deflation of the blood pressure cuff. As a result, the SBP readings acquired for max exertion could have been slightly lower than actual arterial pressures at the maximum exertion timepoint. However, it is unlikely the timing of SBP readings confounded differences seen between the two groups. First, measurements were collected at exactly the same time for both groups. Second, previous studies have shown pressure readings to be relatively constant within the first minute of exercise termination (Al Haddad, Laursen, Chollet, Ahmaidi, & Buchheit, 2011; Becker, Silva, Moreira, & Victor, 2007; Buchheit et al., 2008; Muntner P, He J, Cutler JA, Wildman, & Whelton, 2004; Singh, Rhodes, & Gauvreau, 2008). Third, SBP readings taken for the maximum exertion time point were also lower in the E-PVFM group across the other timepoints as well. Therefore, the method of acquisition for the maximum exertion time point should not have confounded study results.

The second limitation associated with the maximum exertion SBP readings was that only one reading was used to compare group differences, while the average of three readings was used for the pre-baseline and baseline laryngoscopy SBP measurements. However, the averaged readings taken during the two rest conditions were all well within 5-10 mmHg of each other, showing good reliability with the blood pressure cuff and instilling confidence in the maximum exertion SBP readings. The final limitation was the high prevalence of failed SBP readings at the 3-minute post-maximum exertion time point across groups (n = 5 E-PVFM, n = 6 control, respectively). Participants remained on the cycle trainer until their heart rates and blood pressure readings had decreased in order to reduce the risk of dizziness and injury during trainer dismount. However, by the three-minute mark participants became restless on the trainer, thus increasing the

rate of cuff reading failures. Fortunately, since these readings were solely used to monitor safety of the participants and not as outcome parameters, cuff failure at this point was less of a concern. In cases where the cuff readings did fail, the heart rate monitor was used to assess cardiovascular recovery to make sure participants were safe to dismount and leave the hospital premises after completing the study protocol.

4.6 CONCLUSION

Results of this prospective experimental study suggest the best physiological correlates of E-PVFM are anterior glottal angles observed during the inspiratory phase of the respiratory cycle during provocation challenge. The role of expiratory glottal angles and arytenoid pattern responses during provocation for E-PVFM diagnostics require future investigation with larger sample sizes, other PVFM trigger variants, and pathological comparison groups to determine their merit. Overall, study findings highlight the importance of provocation challenge and use of comparative studies involving healthy normal cohorts to identify key laryngeal features indicative of E-PVFM. Finally, trends in sympathovagal response differences between the two groups suggest there is merit to studying the role of the autonomic nervous system in future investigations. The results of this study will likely improve the sensitivity of diagnostic paradigms and overall management of E-PVFM; the study can also be used to drive future investigations into PVFM identification, both from a clinical and etiological perspective.

5.0 MANUSCRIPT #2: PERCEPTUAL FEATURES OF E-PVFM

5.1 ABSTRACT

Introduction: Exercise-induced paradoxical vocal fold motion disorder (E-PVFM) is a condition typically seen in adolescent athletes. Acute E-PVFM episodes are triggered by increased physical demands such as high intensity or extended periods of aerobic activity (e.g., running, swimming). The hallmark clinical features of these acute episodes—paradoxical adduction of the true vocal folds and dyspnea—cause detriments to athletic performance. However, various other features, such as paradoxical supraglottic response (e.g., arytenoid prolapse, epiglottic collapse) and a host of associated symptoms (e.g., cough, dysphonia, throat tightness), have been attributed to E-PVFM presentation as well (Shembel et al., 2017). Unfortunately, the majority of individuals with E-PVFM are initially misdiagnosed with another medical condition, such as exercise-induced asthma, resulting in prolonged mismanagement of the condition (Bernstein, 2014; Traister et al., 2016). The high prevalence of initially unsuccessful identification of E-PVFM is largely due to a lack of consensus in key clinical features that indicate a diagnosis. The dearth of validated quantifiable methods to improve specificity of diagnosis and lack of severity benchmarks also complicate matters. Finally, there is a significant gap in prospective experiments using participants with normal systemic responses to exercise as comparisons to distinguish the "typical" from the "atypical." Mechanisms underlying E-PVFM clinical presentation are also poorly understood, further complicating identification and management of the condition. However, certain temperament qualities such as perfectionism, neuroticism and high stress reactivity have been implicated as the underlying cause (Forrest et al., 2012; Husein et al., 2008).

The objectives of this study were twofold. The first goal was to identify and quantify key symptom presentations in E-PVFM, using normative and atypical perceptual responses to exercise as diagnostic benchmarks. The second goal was to investigate whether stress reactivity plays a role in E-PVFM pathology by comparing temperament differences between participants with and without E-PVFM.

Methods: 27 adolescent athletes (13 E-PVFM, 14 control) were recruited from the Massachusetts Eye and Ear Voice and Speech Laboratory and the greater Boston region. All participants underwent a graded exercise test on a cycle trainer during continuous laryngoscopy; cardiovascular biomarkers were also acquired during the protocol. Prior to the exercise test, participants were asked to rate the severity of their current symptoms experienced at rest using a 0-100 continuous visual analog scale (VAS) and completed the Fear subscale on the Early Adolescent Temperament Questionnaire – Revised (EATQ-R). Participants then rated the same symptoms experienced with rigorous exertion using the 0-100 VAS immediately after the exercise test protocol had been completed.

Results: There were significant group differences in exercise response between patients with E-PVFM and athletic volunteers (control) for inspiratory and expiratory dyspnea (p = .01, respectively). Both groups had significant responses to exercise, compared to baseline, for symptoms of stridor (E-PVFM: p = .01; control: p = .001) and throat tightness (p = .01, respectively). However, there were no significant group differences found between the two cohorts for the latter two symptom parameters. The following symptoms features were not as prevalent amongst the patients with E-PVFM: chest tightness, cough, dysphagia, globus, lightheadedness, limb paresthesia, syncope, systemic fatigue, throat clearing, and dysphonia. Measurements of stress reactivity (suggestive of proclivity towards anxiety) using the EATQ-R Fear subscale were

remarkably similar between the two athletic groups. However, EATQ-R Fear Subscale scores for both groups were significantly higher compared to normative data across typical adolescents in the US population.

Discussion: Participants in both groups got short of breath with exercise, which is to be expected during strenuous physical activity. However, severity ratings on shortness of breath were significantly higher in the E-PVFM group than the control group during these physically demanding tasks. Severity benchmarks indicate that a visual analog scale of 30 out of 100 or higher is a good diagnostic marker for E-PVFM pathology using dyspnea as a biomarker. However, further study is needed with larger sample sizes to confirm this statement. Furthermore, both groups experienced noisy breathing and throat tightness in response to exercise. However, the latter two parameters did not significantly distinguish participants with E-PVFM from those without the condition; these same two parameters were also highly variably in how they were perceived across both groups. Furthermore, the following features: chest tightness, cough, dysphagia, globus, lightheadedness, limb paresthesia, syncope, systemic fatigue, throat clearing, and dysphonia may better reflect other comorbidities common in the E-PVFM population (e.g., asthma, muscle tension dysphonia, anxiety disorders) or may better represent other PVFM variants (e.g., irritable larynx syndrome, psychosomatic-associated PVFM). Finally, similarities on responses to stress reactivity between athletic groups insinuates certain temperaments typically attributed to patients with E-PVFM may instead better reflect temperaments in competitive young athletes, in general.

Conclusion: Study findings highlight the importance of normative comparisons when studying E-PVFM as well as the clinical utility of provocation challenge to improve sensitivity of E-PVFM

diagnosis. Findings also suggest caution when attributing temperament and personality traits to E-PVFM pathogenesis.

5.2 INTRODUCTION

Paradoxical vocal fold motion (PVFM) disorder is a condition that is thought to present primarily as shortness of breath (dyspnea) and has been attributed to airflow obstruction at the level of the larynx (Heimdal et al., 2006). Symptoms are provoked suddenly and acutely by systemic or environmental stimuli. Many other symptoms, including hoarseness, cough, throat clearing, dysphagia, and globus sensation, have all been associated with PVFM as well (Morrison & Rammage, 2010b; Vertigan et al., 2006; Vertigan, Theodoros, Winkworth, & Gibson, 2008; Vertigan, Theodoros, Gibson, & Winkworth, 2007). However, whether these symptoms are *indicative* of PVFM or whether they reflect concomitant pathologies that often co-occur in the PVFM population (e.g., muscle tension dysphonia, chronic cough, asthma) is unknown. Gaps in systematic, prospective study of PVFM, and the dearth of normative studies to compare to and better identify pathology specific to PVFM, has resulted in differential diagnosis based on exclusion. As a result, features axiomatic to PVFM, and severity benchmarks of pathology, are left open to interpretation.

It is therefore not surprising that as many as 90% of individuals with PVFM are initially misdiagnosed (Bernstein, 2014; Newman, Mason, & Schmaling, 1995; Traister, Fajt, Whitman-Purves, Anderson, & Petrov, 2013; Koufman & Block, 2008; MacConnell & Danielsen, 20103.; Mikita & Mikita, 2006; Morris et al., 2006; Nascimento et al., 2013; Tilles & Inglis, 2009).

Unfortunately, these concerns are non-trivial. A delay in correct diagnosis means individuals are mismanaged, on average, for 7.5 years (Bernstein, 2014; Newman et al., 1995; Traister et al., 2013). For example, individuals with an exertional- or exercise-induced PVFM variant (herein referred to as E-PVFM) are often misdiagnosed with exercise-induced asthma (EIA). The first line approach is inhaled corticosteroids to manage symptoms. As symptoms persist, the course of treatment becomes longer and medication dosing becomes higher. Unfortunately, prolonged pharmacological mismanagement can lead to iatrogenic consequences such as osteoporosis, obesity, stunted growth, Cushing's disease, and hypertension in otherwise healthy, young individuals (Christopher et al., 1983; Heinle et al., 2003; Newman et al., 1995; Noyes & Kemp, 2007).

For adolescent athletes with E-PVFM—the cohort most commonly seen in the clinical setting with an exertional trigger variant (Ahrens, Seibt, & Kitz, 2001; Gavin et al., 1998; Landwehr et al., 1996; Sandage & Zelazny, 2004; S. A Tilles, 2003)—protracted mismanagement can also mean missed collegiate scholarship opportunities and can result in withdrawal from sports and the sports community, leading to feelings of isolation and impairment to self-concept (De Guzman et al., 2014; Røksund et al., 2009; Weinberger & Abu-Hasan, 2009; Weinberg & Gould, 2011). Therefore, to help prevent frequent misdiagnosis and mismanagement of the condition, the primary goal of this study was to quantify inspiratory dyspnea and compare severity ratings between athletic adolescents with and without E-PVFM as means to improve diagnostic benchmarks for pathology. The second goal was to identify other perceptual features relevant to the E-PVFM cohort. These additional clinical features representing the E-PVFM cohort were also compared to typical sensations individuals without E-PVFM experience during exercise to improve diagnostic specificity.

In addition to the gap in identifiable features indicative of PVFM, creating diagnostic challenges, the underlying mechanisms involved in PVFM etiology are also largely unknown. Although previous literature has frequently alluded to temperament and mental/mood disorders as the cause (Brown M., Merritt, & Evans, 1988; Earles, Kerr, & Kellar, 2003; Guglani, Atkinson, Hosanagar, & Guglani, 2014; Husein et al., 2008; Leo & Konakanchi, 1999; Mobeireek, Alhamad, Al-Subaei, & Alzeer, 1995; Weinberger & Doshi, 2017)—especially in young adolescent female athletes—the theory is largely unsubstantiated due to lack of empirical evidence. PVFM induced by exertional activity has been deemed a form of somatization due to the high-achieving, competitive, and anxious nature characterizing individuals with the exercise-induced variant (Leo & Konakanchi, 1999; Maschka et al., 1997). However, it could just as easily be that these traits are characteristic of any athlete with a competitive drive and proclivity towards perfectionism (trait anxiety) (Bartulovic et al., 2017; Hill & Madigan, 2017; Weinberg & Gould, 2011). Conversely, perceptions of uneasiness and inadequacy could be a *consequence* of PVFM symptoms that are causing detriments to athletic performance (state anxiety) (Hicks et al., 2008; Mathers-Schmidt, 2001; Nascimento et al., 2013). If there is, in fact, a relationship between PVFM and psychopathology, determining whether the relationship is causal, consequential, or correlational is a worthwhile pursuit to improve management of the condition. Therefore, to determine the merit of psychopathology as a mechanism in PVFM for future pathoetiological studies, the third goal of this study was to compare temperament (stress reactivity) in competitive young athletes, with and without E-PVFM.

To accomplish these study objectives, participants in the E-PVFM group were asked to identify which clinical symptoms they experienced during athletic activity from a list of symptoms associated with PVFM across the condition spectrum found in the current literature (see Table 5-1

for complete list of symptoms; also see Shembel et al., 2017, for details on working comprehensive taxonomy framework). Two groups of competitive adolescent athletes, with and without E-PVFM, were then both asked to quantify self-perceived severity of clinical features using the most frequent symptoms reported by the E-PVFM group on a 0-100 continuous visual analog scale (VAS) during rest (baseline) and exercise challenge. Participants were also asked to complete the *Fear* subscale of the Early Adolescent Temperament Questionnaire- Revised (EATQ-R) to target anxiety-related temperament (i.e., stress reactivity) (Ellis & Rothbart, 1999).

5.3 METHODS

5.3.1 Participants

Twenty-seven adolescent athletes (n = 13 E-PVFM; n = 14 control) were recruited for the study. Participants were all physically active, competitive athletes who participated in organized sports. Individuals with suspected E-PVFM were recruited from the Voice and Speech Laboratory at Massachusetts Eye and Ear Infirmary (MEEI) at the time of their initial consultation visit with the Speech-Language Pathology team. Participants in the control group were recruited from local schools and sports teams in the New England region. Participants in both groups were eligible for the study if they were between the ages of 12-18 years and played competitive sports at least three times a week for a minimum of 40 minutes per athletic session. Potential recruits from the patient population at MEEI were included in the experimental group if they scored at least a 10 out of 40 on the Dyspnea Index (Gartner-Schmidt et al., 2014) and if laryngeal patterns on laryngoscopy involved "atypical" responses (e.g., paradoxical adduction of the vocal folds; prolapse or quivering

of the arytenoids) either at rest or during exercise (see Shembel et al., 2017 for specifics on PVFM laryngeal categorization). Potential participants had all undergone extensive medical workups with specialists (e.g., ENT, GI) prior to their initial consultation at the Voice and Speech Laboratory to rule out other pathology that could account for their dyspneic-related symptoms (e.g., asthma, allergies). Participants were included if they had no asthma (defined as FEV1 >80% predicted), or well-managed asthma (defined as FEV1 >80% predicted with their inhaler during methacholine challenge). The decision to include participants with well-controlled exercise-induced asthma into the experimental group was driven by the higher prevalence of co-occurring asthma in the E-PVFM population (30-40% comorbidity). Since bronchodilators (inhalers) temporarily open the airways, any symptoms related to dyspnea with FEV1 >80% will be reflective of E-PVFM and not exercise-induced asthma (Balkissoon & Kenn, 2012; Collett et al., 1983; England et al., 1985; Higenbottam, 1980; Martin et al., 1987; O'Donnell et al., 1987; Patterson & O'Connell, 1994).

Athletic volunteers were eligible for the control group if they had not previously experienced dyspnea detrimental to athletic performance within the past 6 months, and if they scored less than 7 out of 40 on the Dyspnea Index. Participants were excluded if they had a history of previously diagnosed obstructive pulmonary diseases (e.g., asthma).

Participants in both groups were excluded if they had any of the following in their medical history: (1) developmental, behavioral, or cognitive disorders that would make following directions for the cycling challenge difficult, (2) neuromuscular disorders that could affect exercise response, (3) cardiovascular conditions that would make the exercise challenge unsafe, (4) intolerance to flexible nasoendoscopy, and (5) structural or anatomical abnormalities that occluded more than a third of the upper airways at rest. All eligible participants were asked to refrain from exercise or caffeine consumption within 2 hours prior to their appointment, and to wear

comfortable clothing and closed toed shoes (e.g., sneakers) that would allow them freedom of movement for exercise. Participants with well-managed asthma in the E-PVFM group were also asked to bring their inhaler with them to the appointment.

5.3.2 Procedures

Once consented, participants rated severity of symptoms they experienced at the *present* moment using a 0-100 continuous visual analog scale (VAS), first at baseline (x2; pre-baseline and baseline laryngoscopy) and then once at maximum exertion (bike challenge) (see Table 5-1 for complete list of symptoms). In addition to the symptoms in Table 5-1, participants were also asked to rate the severity of their leg fatigue at rest and maximum exertion. This parameter was used as a positive control foil to confirm consistency in responses between the two groups. The list of symptoms and positive control foil were randomly presented to participants to prevent order effect.

Table 5-1. List of PVFM-related symptoms, based on a comprehensive literature review by Shembel et al., 2017

Perceptual Symptom Parameters
Chest tightness
Cough
Dysphagia (swallowing complaints)
Globus sensation
Lightheadedness/dizziness
Limb paresthesia
Shortness of breath with expiration
Shortness of breath with inspiration
Stridor (noisy breathing)
Syncope
Systemic fatigue
Throat clearing
Throat tightness/constriction
Voice complaints (dysphonia/hoarseness)

Each symptom had a corresponding 0-100 continuous horizontal line below it. Participants were asked to place a tick mark representing respective levels of severity for each parameter, using a Fire HD-10 touch-screen tablet (Amazon Ltd.) and customized VAS, created at www.surveygizmo.com (see representative example in Figure 5-1). The most common symptoms reported in the E-PVFM group were then statistically analyzed between groups and conditions to determine perceptual differences between individuals with and without PVFM, specific to the exertion PVFM variant.

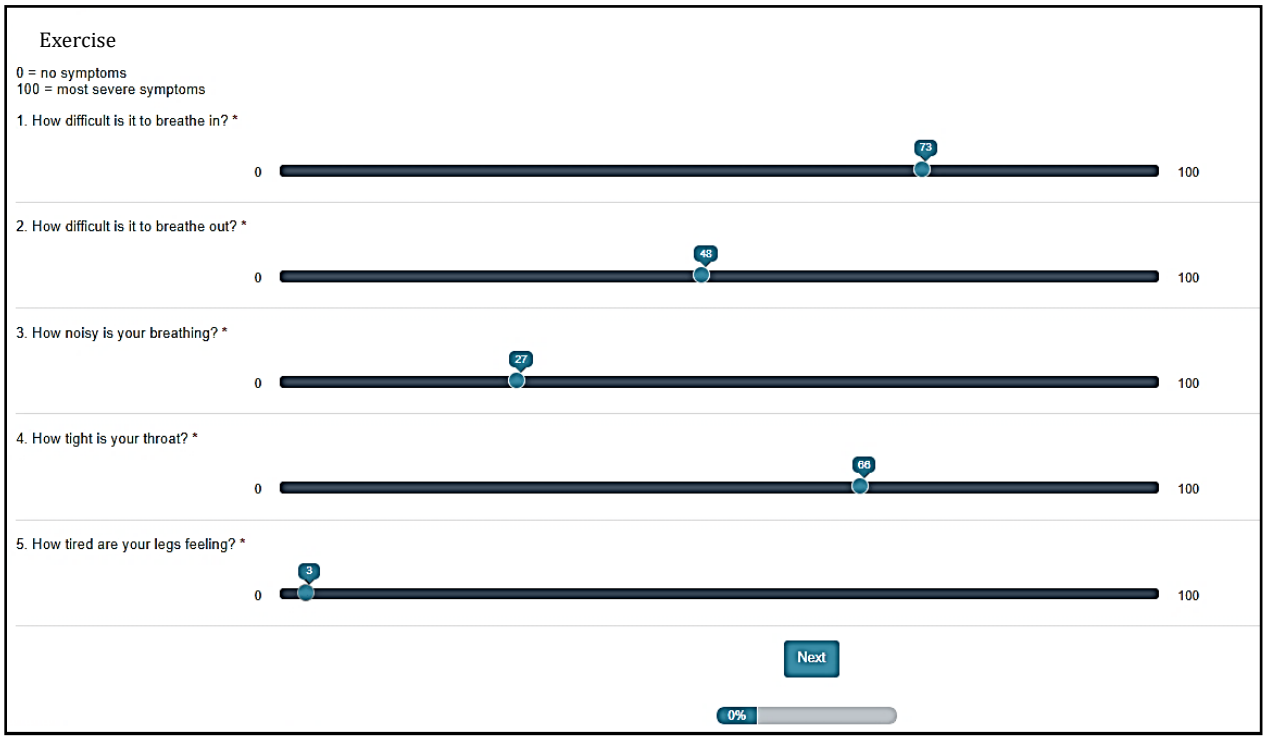


Figure 5-1. Example of VAS symptom severity rating tablet interface. Figure not to scale.

After each participant completed baseline severity ratings, but prior to completing severity ratings with exertion, participants were asked to respond to questions on the Fear Subscale of the Early Adolescent Temperament Questionnaire – Revised (EATQ-R) (Ellis & Rothbart, 1999) using the same digital touch-screen tablet. The EATQ-R, overall, measures different temperament

constructs such as self-regulation and emotionality. The Fear subscale on the EATQ-R, specifically, measures perceived levels of unpleasantness and negative affect associated with anticipation of stressful events (i.e., stress reactivity) (Ellis & Rothbart, 1999). This subscale is thought to correlate with high levels of anxiety and neuroticism in adolescents (Muris & Meesters, 2009; Snyder et al., 2015).

Once baseline ratings and responses on the Fear EATQ-R subscale were completed, a heart rate monitor (Polar H7 Bluetooth Heart Rate Sensor & Fitness Tracker) and blood pressure cuff (Welch Allyn Spot Vital Signs LXi) were each placed on the participant's chest and right arm, respectively, to monitor vitals. Oxymetazoline (nasal decongestant) was then administered into the nostrils bilaterally in accordance with standard of care procedures at Massachusetts Eye and Ear Voice and Speech Laboratory. Participants were trained to quantify levels of physical effort using a perceived exertion scale (1-8) while vigorously riding a stationary bike (trainer) (1 = no exertion, 8 = anaerobic activity that cannot be sustained for longer than a minute) and were told they would be encouraged to continue pedaling until maximum, vigorous exercise had been reached (8 on the exertion scale). Patients with suspected E-PVFM were instructed to give a "thumbs up" sign when they experienced symptoms representative of complaints they typically experienced during their respective sport(s) or other competitive athletic activities. Once participants communicated understanding, the height and seat of the stationary bike (SF-B1203 Indoor Cycle Trainer) was adjusted to each participant's configuration. Target ergonomics was a slight bend at the knee joint (10-15° angle) and comfortable extension of the arms on the handlebars for stability (Paridon et al., 2006; Pollock, Wilmore, & Fox, 1984).

Participants sat on the bike once it had been adjusted to meet their specifications. Surgical lubricant jelly (E-Z Jelly, Medline Industries, Inc., Mundelein, IL) was placed on the tip of the

flexible endoscope (KayPENTAX EPK-1000, Kay Elemetrics Corp., Lincoln Park, NJ) and the endoscope was then passed through the naso- and oro-pharynx into the laryngeal vestibule. Once the camera was in place, the larynx was briefly visualized with halogen light to rule out structural or organic anomalies that could explain dyspneic symptoms experienced with exertion. Participants again rated symptoms on the VAS for later pre-baseline comparisons and to preemptively account for potential differences in symptom presentation with introduction of the endoscope into the laryngeal vestibule. Videorecordings of laryngeal movement (*n*Stream G3, Image Stream Medical) were then initiated with cycle challenge (Continuous Exercise Laryngoscopy test [CLE-test]; refer to Heimdal et al., 2006 and Olin et al., 2016 for details). The protocol involved progressive resistance increments (one 360° rotation with lever) every 30 seconds at 50-110 rpms on a stationary bike with concurrent flexible laryngoscopy. For the control group, resistance increased until participants perceived an 8 on the exertion scale, at which point 30 additional seconds of laryngeal movement was visualized to confirm no paradoxical movement was seen on the laryngoscopy video and to parallel the protocol with the E-PVFM group. Once participants in the control group had reached maximum exertion, the exercise protocol was terminated and the endoscope was removed. For participants with suspected E-PVFM, resistance increased incrementally every 30 seconds until an E-PVFM episode was induced. At the point of induction, 30 additional seconds of the provoked episode was recorded before participants in the E-PVFM were asked to cease pedaling. Rescue breathing techniques were then implemented, as needed, to mitigate symptoms of the attack after the cycle protocol had been terminated (see CliftonSmith & Rowley, 2011; Mathers-Schmidt, 2001; Sandage & Zelazny, 2004 for details). Presence of E-PVFM in the experimental group was confirmed based on (1) patient report ("thumbs up" to indicate E-PVFM symptoms) and (2) concurrent glottic and/or supraglottic

responses seen on videoendoscopy during cycling challenge. An E-PVFM episode was considered present if both patient perceptions of symptoms and medial laryngeal responses/glottic obstruction with exercise challenge occurred. Presence of atypical laryngeal response patterns were determined by two licensed speech-language pathologists at the Voice and Speech Laboratory at Massachusetts Eye and Ear. As soon as participants (in both groups) had stopped pedaling on the trainer, they were immediately asked to rate the severity of symptoms they experienced during maximum exertion on the tablet for the third and final time. Finally, using a 1-10 scale (1 = no symptoms, 10 = most severe episode experienced), participants in the E-PVFM group were asked to rate the severity of the episode they experienced with the exercise challenge, as compared to symptoms typically experienced with their respective sports/athletic activities. Participants were also asked to indicate (yes/no) whether the symptoms they experienced with the exercise challenge were representative of symptoms they typically experienced on the court or field.

Symptom severity scores (1-100 continuous VAS) acquired during rest conditions (pre-baseline and baseline laryngoscopy) and exercise challenge, as well as EATQ-R Fear subscale scores, were extracted from the tablet and raw data were placed into an Excel spreadsheet for later data reduction and analysis. Kruskal Wallis H tests, Mann-Whitney U tests, and Wilcoxon Sign-Rank tests with Bonferroni corrections were conducted on the common symptoms reported in the E-PVFM group (inspiratory dyspnea, expiratory dyspnea, stridor, and throat tightness) to determine group (E-PVFM, control) and condition (rest, exercise) differences on these parameters. An independent samples t test was also conducted for the EATQ-R Fear Subscale. Statistical analysis used for each outcome parameter will be discussed in detail in the Results section.

5.4 RESULTS

5.4.1 Demographics

The mean age of participants was 14.46 years (*SD* = 1.94) for the E-PVFM group and 16.87 (*SD* = 1.19) for the control group. There were 9 females and 4 males in the E-PVFM group, and 9 females and 5 males in the control group. The 2:1 prevalence in female-to-male ratio in the E-PVFM group is consistent with previous literature showing E-PVFM affects twice as many females as males (as compared to the 3-5 times greater female prevalence in other types of PVFM) (Olin et al., 2015). All participants played competitive organized sports and were heavily involved in other athletic extracurricular activities (see Table 5-2 for details). Participants in the E-PVFM group participated in sports an average of 5.57 times per week (*SD* = 1.14); participants in the control group played sports an average of 5.83 times per week (*SD* = 0.96). Average length of time per athletic session was 103.46 minutes (SD = 31.32) for the E-PVFM group and 95.67 minute (SD = 42.80) for the control group. Average level of self-reported physical effort exerted during regularly scheduled athletic activities was 8.08 for the E-PVFM group (*SD* = 1.04) and 7.47 for the control group (*SD* = 1.25) (1-10 scale, 1 = no effort and 10 = maximum effort). Mean Dyspnea Index scores for the E-PVFM group was 25.15 (SD = 5.16) and 2.60 (SD = 2.90) for the control group. The mean length of time to maximum exertion during the study's exercise challenge was 277.00 seconds (*SD* = 85.87 sec.) in the E-PVFM group and 265.71 seconds (*SD* = 48.48 sec.) in the control group. See Table 5-2 for a summary of demographic findings.

Table 5-2. Demographics of E-PVFM and Control Groups

Group	Age	Gender	Aerobics/Sports	Times/ Week	Session Length (min.)	Effort Level (1-10)	Dyspnea Index	Time to max exertion (sec.)
E-PVFM	14.46 ±1.94	9 F 4 M	1 Basketball 1 Crew 3 Cross country/Track & Field 1 Frisbee 1 Ice hockey 2 Lacrosse 1 Skiing 5 Soccer 3 Softball/Baseball 2 Squash 1 Swimming	5.75 ±1.14	103.46 ±31.32	8.08 ±1.04	25.15 ±5.16	277.00 ±85.87
Control	16.87 ±1.19	9 F 5 M	2 Crew 9 Cross country/ Track & field 1 Cycling 1 Field hockey 1 Ice hockey 1 Dancing (aerobic) 2 Skiing 3 Soccer 1 Softball/Baseball 1 Swimming 3 Tennis	5.83 ±0.96	95.67 ±42.80	7.47 ±1.25	2.60 ±2.90	265.71 ±48.48

The screening protocol revealed that within the E-PVFM group, the average reported length of time to onset of E-PVFM episodes experienced when playing sports outside of the clinical setting (e.g., on field or court) was 5.78 minutes (range 30 seconds – 15 minutes) and average resolution of symptoms was 16.38 minutes (range 2 minutes – 2 hours). All 13 participants had been prescribed a trial course of inhalers prior to their initial consultation at the Mass Eye and Ear Voice and Speech Laboratory. The average improvement in E-PVFM-related symptoms with inhalers was 29.58% (range 0-85%). Of the 13 participants, 9 of the participants reported less than 50% improvement with inhalers.

The prevalence of concomitant asthma found in 38% [5/13] of participant in the E-PVFM group (confirmed with pulmonary function testing) is consistent with previous literature showing asthma co-occurs with E-PVFM 30-40% of the time (Christopher & Morris, 2010; Hicks et al., 2008; Hoyte, 2013). Diagnosed environmental allergies were also prevalent in 38% (5/13) of patients with E-PVFM in the present study. Gastroesophageal reflux disease (GERD) was prevalent in 15% (2/13) of E-PVFM participants. Clinically diagnosed generalized anxiety disorder was found in 8% of E-PVFM participants (1/13). Three out of 13 participants (31%) in the E-PVFM group reported extreme temperatures and environment (e.g., heat, cold, dry air, humidity) further amplified E-PVFM symptoms they typically experienced with exertion. E-PVFM episodes were induced with cycle challenge in ninety-two percent (92%) of participants (12/13) using the continuous laryngoscopy exercise (CLE) test protocol. Positive provocation, defined by patient-reported symptoms and concurrent laryngeal response pattern changes, was not evoked in one of the thirteen participants in the E-PVFM group. Mean severity of E-PVFM symptoms experienced with cycle challenge (compared to temporal parameters of typical sports-induced episodes, previously noted) was 7.30 (range: 5-9; scale: 1 = no symptoms, 10 = most severe episode experienced). Qualitatively, all participants reported symptoms during the cycle challenge were representative of symptoms they typically experienced during athletic practices or competition.

Twelve out of 13 participants reported inspiration was typically more challenging then expiration during their typical athletic activities (e.g., out on the field or court), although all participants in the E-PVFM group experienced some levels of shortness of breath during both inspiratory and expiratory cycles. The 13th participant reported expiration and inspiration were equally challenging. The four bolded symptoms in Table 5-3—inspiratory dyspnea, expiratory

dyspnea, stridor, and throat tightness—were the most prevalent features reported in the E-PVFM cohort. Therefore, the severity of these symptoms was compared between groups with and without E-PVFM and statistically analyzed to determine group and condition differences. Severity of leg fatigue was also statistically analyzed to confirm perceptual consistency between groups and ensure that groups reached equivalent exertion levels. The other (non-bolded) symptoms in Table 5-3—chest tightness, cough, dysphagia, globus pharyngeus, dizziness, paresthesia of the limbs, systemic fatigue, throat clearing, and voice complaints—were less prevalent in the E-PVFM cohort. Therefore, severities of these features were not rated or statistically analyzed between the two groups.

Table 5-3. List of Symptoms Associated with PVFM Across the Symptom Complex and Prevalence of Reported Symptoms in E-PVFM Group

Perceptual Symptom Parameters	# (%) of E-PVFM Participants
Chest tightness	3 (23%)
Cough	1 (8%)
Dysphagia (swallowing complaints)	1 (8%)
Globus sensation	1 (8%)
Lightheadedness/dizziness	2 (15%)
Limb paresthesia	1 (8%)
shortness of breath with expiration	**8 (60%)**
shortness of breath with inspiration	**13 (100%)**
Stridor (noisy breathing)	**6 (46%)**
Syncope	0 (0%)
Systemic fatigue	1 (8%)
Throat clearing	2 (15%)
Throat tightness/constriction	**6 (46%)**
Voice complaints (dysphonia/hoarseness)	2 (15%)

5.4.2 Symptom Severity Ratings

5.4.2.1 Inspiratory Dyspnea

On average, participants in the E-PVFM group reported greater dyspnea with inspiration on the 0-100 continuous VAS at both pre-baseline[21] (*M* = 7.46, *SD* = 17.78) and exercise (*M* = 62.92, *SD* = 33.08) conditions, compared to control participants (*M* = 0.57, *SD* = 1.09; *M* = 33.50, *SD* = 23.74, respectively) (baseline Cohen's *d* = 0.55; exercise Cohen's *d* = 1.02) (Figure 5-2). Statistically, the data violated assumptions of normality and variance, requiring nonparametric statistical analysis. Therefore, the Kruskal-Wallis H Test was performed to determine whether there were significant group differences in raw VAS scores at rest and exercise. Wilcoxon signed-rank tests were also performed to determine whether there were significant differences on raw VAS scores between rest and exercise conditions across the groups. Mann-Whitney U Tests were performed to determine whether there were significant differences in *magnitude* of change from rest to exercise conditions between the two groups. Results showed significantly higher ratings of inspiratory dyspnea (raw scores) during exercise as compared to baseline in both the E-PVFM ($p = .002$) and control groups ($p = .001$), per the Wilcoxon signed-rank test. There were also significant raw score differences between groups on inspiratory dyspnea with the exercise challenge ($p = .01$) but not baseline rest ($p = .09$), as determined by Kruskal-Wallis H tests. However, no significant differences were seen in magnitude of change between groups ($p = .07$).

[21] Pre-baseline and baseline laryngoscopy severity ratings were highly similar between the two conditions on all symptom parameters and were therefore not statistically analyzed. The baseline (rest) condition severity ratings were analyzed using the pre-baseline ratings.

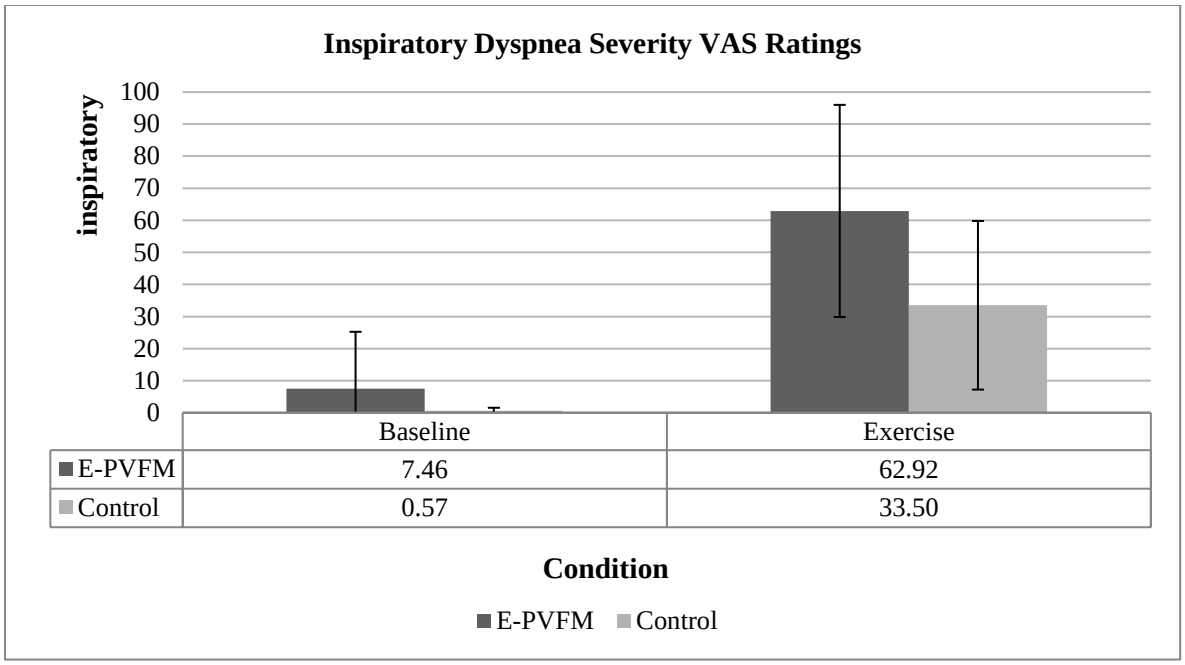


Figure 5-2. Inspiratory dyspnea (raw scores) group differences at rest and exercise

5.4.2.2 Expiratory Dyspnea

On average, participants in the E-PVFM group had higher perceptions of dyspnea (raw scores) with expiration both at baseline (M = 7.15, SD = 17.83) and during exercise (M = 48.62, SD = 34.61), as compared to control participants (M = 0.21, SD = 0.65; M = 34.61, SD = 26.78, respectively) on the VAS (baseline Cohen's d = 0.55; exercise Cohen's d = 0.45) (Figure 5-3). Statistically, the data violated assumptions of normality and variance, requiring the same nonparametric analyses as for inspiratory dyspnea. Results showed significantly higher ratings of expiratory dyspnea (raw scores) during exercise as compared to baseline in both the E-PVFM and control groups (p = .003, respectively), per the Wilcoxon signed-rank test. There were significant raw score differences between groups on expiratory dyspnea with the exercise challenge (p = .01) and baseline rest (p = .02), as determined by Kruskal-Wallis H tests. However, no significant differences were seen in magnitude of change between groups (p = .15).

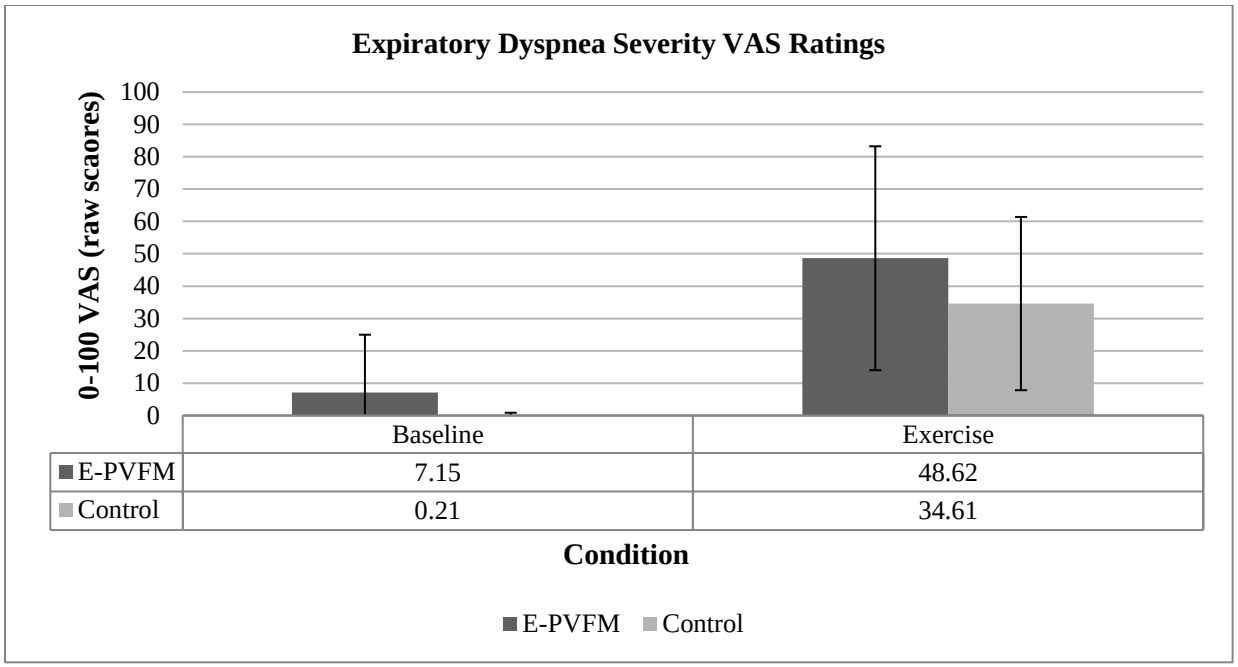


Figure 5-3. Expiratory dyspnea (raw scores) group differences at rest and exercise

5.4.2.3 Stridor

On average, severity levels of self-reported stridor (noisy breathing during inspiration) were similar between groups (Figure 5-4) (baseline Cohen's d = 0.12; exercise Cohen's d = 0.002). Statistical analysis showed no statistically significant differences between groups for the rest and exercise conditions (raw scores) or magnitude of change across conditions ($p > .05$), as assessed by Kriskal-Wallis H test and Mann-Whitney U tests, respectively. However, significant

differences were seen between baseline rest and exercise conditions in both the E-PVFM (p = .01) and control groups (p = .001), as assessed by Wilcoxon signed-ranks tests.

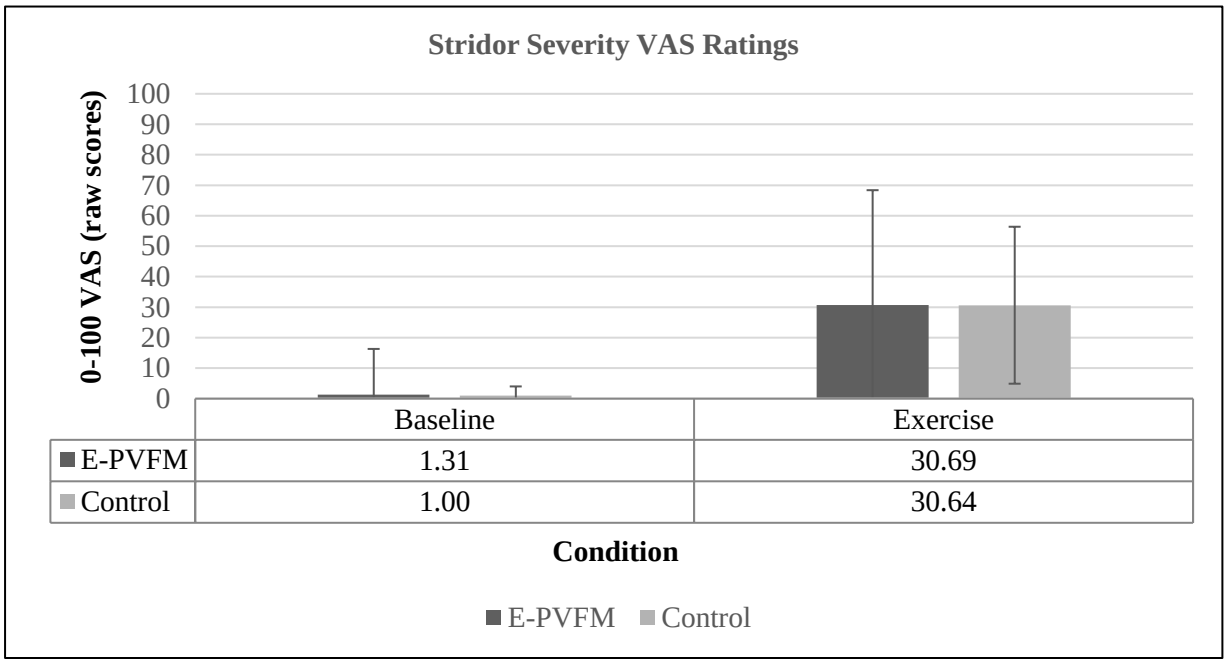


Figure 5-4. Stridor (raw scores) group differences at rest and exercise

5.4.2.4 Throat Tightness

On average, participants in the E-PVFM group had higher perceptions of throat tightness both during baseline (M = 9.31, SD = 15.05) and during exercise (M = 41.08, SD = 37.57) conditions, as compared to control participants (M = 0.21, SD = 0.58; M = 20.14, SD = 21.64, respectively) on the VAS ratings (baseline Cohen's d = 0.85; exercise Cohen's d = 0.68) (Figure 5-5). However, it is important to note substantial variation in responses within each group (as shown by large standard deviations). A series of nonparametric tests were performed to determine whether there were statistically significant differences in raw scores and magnitude of change across conditions between the two groups, due to violations of normality and variance assumptions. There were no statistically significant differences on throat tightness raw scores between groups in either baseline

or exercise conditions ($p > .05$) or differences in magnitude of change across conditions ($p > .05$), as assessed by Kriskal-Wallis H test and Mann-Whitney U tests, respectively. Significant differences were seen, however, between baseline rest and exercise conditions in both the E-PVFM and control groups ($p = .01$, respectively), as assessed by Wilcoxon signed-ranks tests.

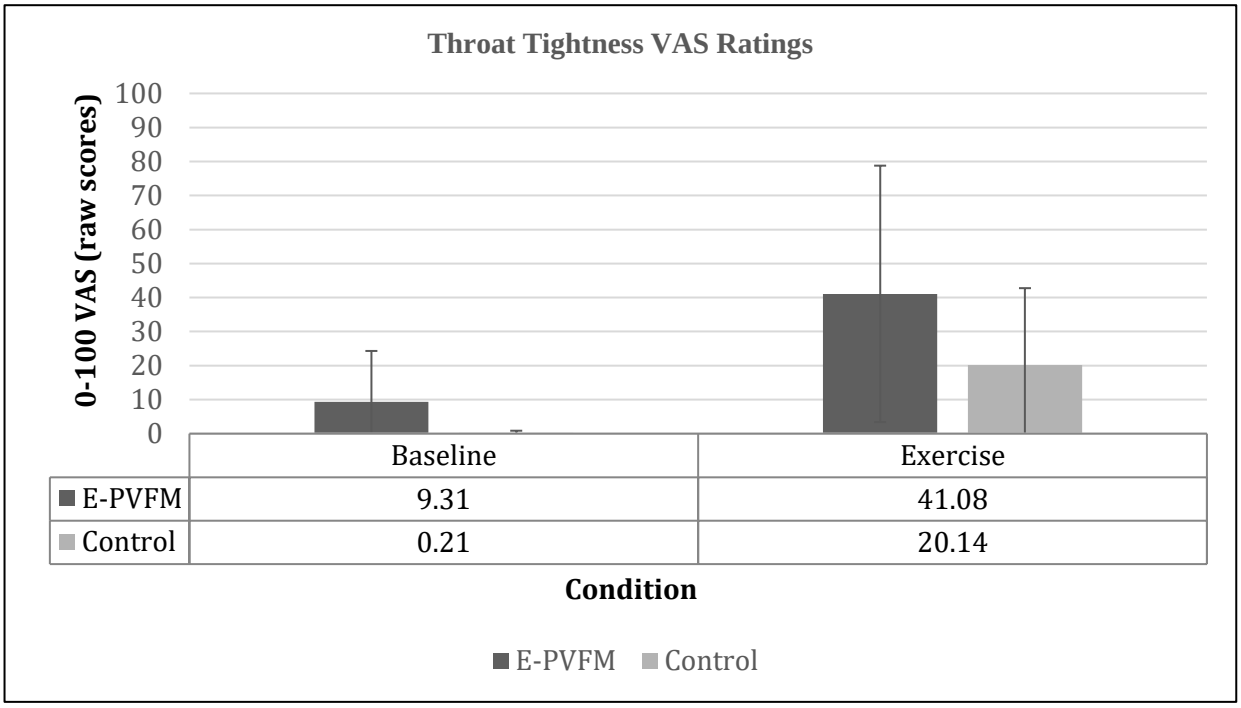


Figure 5-5. Throat tightness (raw scores) group differences at rest and exercise

5.4.2.5 Leg Fatigue

Results on self-reported VAS ratings of leg fatigue between groups and across conditions showed that the groups were equivalent in physical fitness and experienced similar perceived exertion levels. Specifically, participants in the E-PVFM group had similar perceptions of leg fatigue (M = 5.54, SD = 11.19) to control participants (M = 4.79, SD = 9.83) at baseline. Groups were also similar during maximum exertion (E-PVFM: M = 57.54, SD = 33.14; control: M = 63.43, SD = 26.83) (baseline Cohen's d = 0.07; exercise Cohen's d = 0.20) (Figure 5-6). Statistical analysis

showed no significant differences between groups for either rest or exercise (raw scores) ($p > .05$), as assessed by Kruskal-Wallis H tests. Magnitude of change across conditions was also similar between groups ($p > .05$), as assessed by Mann-Whitney U test. Results showed both groups experienced significantly more leg fatigue during maximum exertion, as compared to baseline rest (E-PVFM: $p = .002$; control: $p = .001$), as assessed by Wilcoxon Signed-Rank Test.

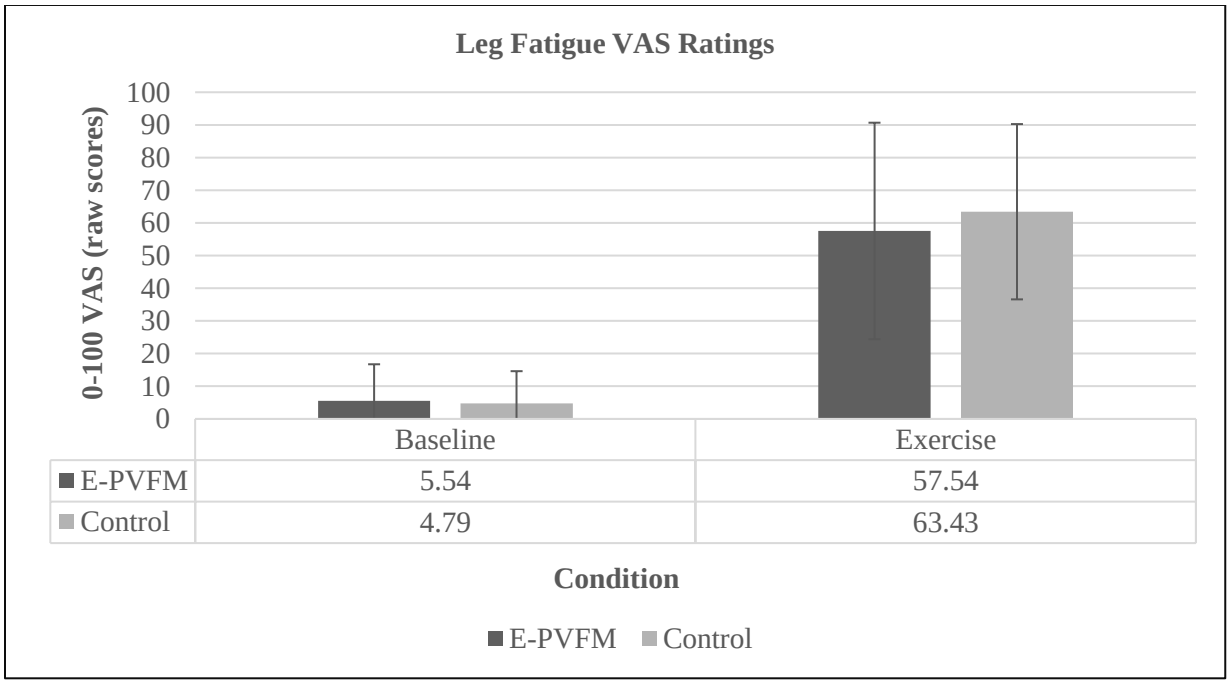


Figure 5-6. Leg fatigue (raw scores) group differences at rest and exercise

5.4.3 Temperament and Stress Reactivity (EATQ-R Fear Subscale)

An independent samples *t* test was conducted to determine if there were significant differences in the EATQ-R Fear subscale between E-PVFM and control groups. There was one outlier in the data, as assessed by boxplot. EATQ-R Fear subscale responses were normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$) and assumption of homogeneity was met, as assessed by Levene's test for equality of variances ($p = 0.97$). EATQ-R Fear subscale scores were slightly

higher in the E-PVFM group (M = 14.23, SD = 4.69) than the control group (M = 12.64, SD = 4.48). However, these group differences were not statistically significant, *mean difference* = 1.59, 95% CI [-2.05, 5.22], $t(25) = 0.90$, $p = 0.37$, $d = 0.35$. Interestingly, group differences between competitive athletes in the present study and the general adolescent population (M = 2.65, SD = 0.77)—based on previously normed epidemiological studies on the EATQ-R—did show statistically significant differences amongst the E-PVFM, athletic control, and general population cohorts, respectively ($p < 0.001$) (E-PVFM group versus general population: $d = 3.45$; control group versus general population: $d = 3.11$) (Muris & Meesters, 2009).

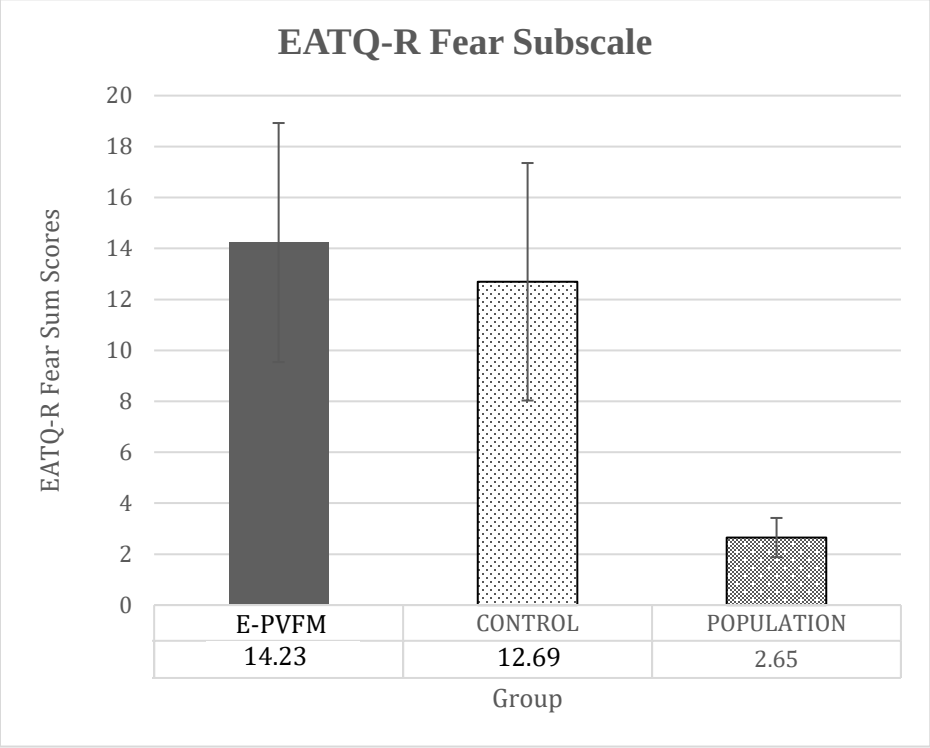


Figure 5-7. Study group and general population EATQ-R Fear Subscale Scores

5.5 DISCUSSION

Dyspnea (inspiratory and expiratory) was the most commonly reported symptom in the E-PVFM group, with the greatest group differences. Qualitatively, all patients in the E-PVFM group reported they experienced dyspnea severe enough to cause detriments to athletic performance. Quantitatively, there were significant group differences on dyspnea severity scores in response to exercise challenge between participants with and without E-PVFM, where patients with E-PVFM reported significantly higher dyspnea. From the list of symptoms thought to indicate PVFM, dyspnea appears to best correlate with the exertion-induced PVFM cohort. Interestingly, participants with E-PVFM also reported sensations of dyspnea at rest before the exercise provocation challenge was initiated. These findings were significantly higher at baseline rest for expiratory dyspnea but not inspiratory dyspnea. The higher sensations with dyspnea patients with E-PVFM experience already experience at rest may be amplified during exercise (see Figure 5-8 for schematic representation of magnitude change differences from rest to exercise between groups), Higher dyspnea experienced at rest could point to another mechanism in additional to, or instead of the larynx, that could be contributing to E-PVFM symptoms (e.g., accessory respiratory muscle tension). Or the findings could indicate different thresholds to laryngeal pattern responses represented in Figure 5-8 (e.g., somatosensory threshold dysfunction). To summarize, the following diagnostic benchmarks can be used to increase confidence in inclusion criteria and improve accuracy of E-PVFM diagnosis: greater than (a) 30/100 on the VAS with strenuous exercise, (b) 20/40 or more on the Dyspnea Index, and (c) presence of stridor and throat tightness during exercise.

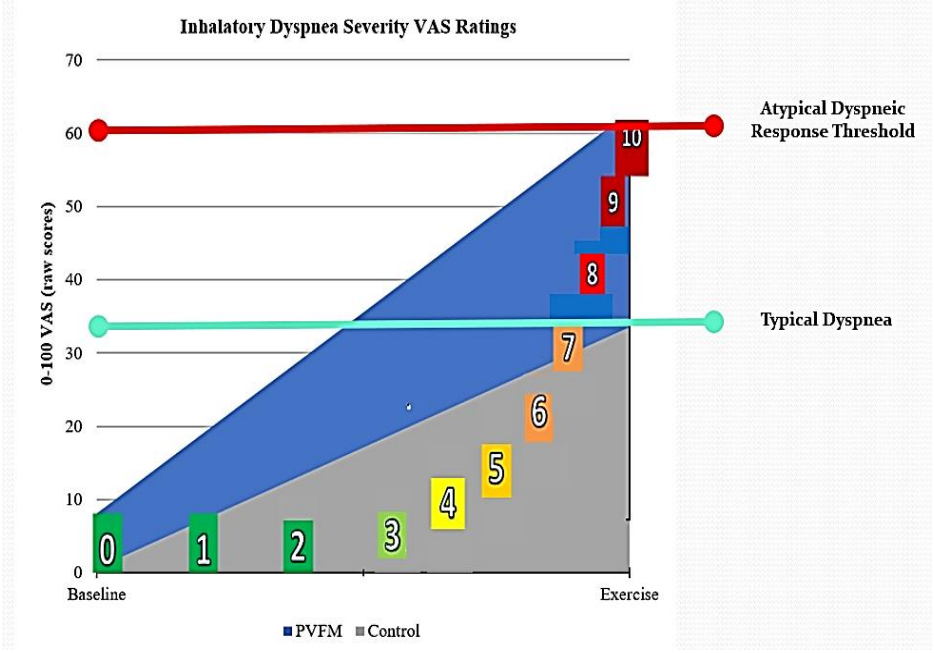


Figure 5-8. Magnitude of response differences between groups on dyspnea severity at rest and exercise. Patterns suggest other mechanisms may contribute to symptoms experienced during asymptomatic periods, such as respiratory musculoskeletal inefficiencies outside the larynx or somatosensory integration dysfunction within the larynx.

It is important to note that the mere *presence* of dyspnea should not be used as a diagnostic indicator, since both groups experienced dyspnea with exercise. Rigorous physical activity causes shortness of breath, regardless of aberrant laryngeal breathing patterns or athletic abilities (who amongst us has not been winded running up a hill or booking it after a bus?). Furthermore, many other disease processes (e.g., asthma, heart disease) cause dyspnea. Therefore, future studies with larger cohorts are needed (n > 30) to better identify *benchmarks* for pathology, using perceptions of dyspnea during provocation challenges as an outcome parameter. These severity cutoff scores can more accurately identify patients with PVFM, appraise treatment outcomes, and identify appropriate cohorts for future studies.

The second most common set of symptoms reported in the E-PVFM group (from the list of PVFM-related symptoms) were stridor and throat tightness. Qualitatively, findings showed

stridor and throat tightness occurred variably across individuals in both groups during rigorous physical activity. Quantitatively, severity of responses on these two parameters increased with exercise in both groups, with no significant differences seen between groups. Results suggest perceptions of stridor and throat tightness may have more to do with the physiological demands athletes place on their bodies, in general, and less to do with a PVFM diagnosis, specifically. However, further study with larger sample sizes are needed to better identify the utilization of these two parameters. High prevalence of dyspnea, throat tightness, and stridor symptoms suggest these features may be more common to the E-PVFM variant. The other, less common features (e.g., cough, dysphonia), may better reflect other PVFM trigger variants (e.g., irritants), other types of PVFM (e.g., irritable larynx syndrome), or other concomitant pathologies (e.g., chronic cough, muscle tension dysphonia, asthma).

Finally, results on the EATQ-R Fear subscale suggest athletes with E-PVFM may have analogous temperaments to other competitive athletes. Extra caution should be taken in the future so as not to *assume* psychopathology to be the cause of E-PVFM. Fortunately, the study of perceptual patterns across different presentations of laryngeal breathing disorders *could* help guide future etiological investigation. Objective, empirical study using such a holistic approach can help us better identify underlying systems that could be responsible for PVFM symptomology. For example, increased levels of dyspnea and throat tightness in E-PVFM, especially during asymptomatic, non-provoked periods, could point to a disrupted somatosensory system. Or, because the respiratory system involves numerous skeletal muscles in the head and neck that help us breathe, the issue could be musculoskeletal. Just as leg muscles can become tight and tethered with repetitive use (e.g., endurance running) causing decrements to athletic performance, so can accessory muscles of the upper airways with chronic heavy exertion.

It is easy to reduce the respiratory system to a series of tubes for gas exchange. However, we often forget about all the tiny, intricate neck/throat muscles that facilitate respiration. The palatoglossus and palatopharyngeus muscles, for example, regulate respiratory rate and airway resistance via changes to oropharyngeal configuration. The pharyngeal constrictors (superior, middle, and inferior) regulate expiratory flow (de Carlos et al., 2013; Dempsey & Pack, 1995; Mathew & Sant'Ambrogio, 1988). Within the larynx itself, the intrinsic laryngeal adductors (thyroarytenoid, intrarytenoids, and lateral cricoarytenoids) and abductor (posterior cricoarytenoid muscle) work in tandem for each inspiratory and expiratory phase of the respiratory cycle. During rigorous exercise, these laryngeal muscles must also coordinate more closely with extrinsic laryngeal muscle elevators (styloglossus, genioglossus, and stylopharyngeas) to increase airway patency (Hillel, 2001; Mathew & Sant'Ambrogio, 1988). In general, all of these head and neck muscles must work together for optimal respiratory coordination and support. Tethered/tight muscles—potentially perceived as throat constriction—from repetitive, high caliber physical activity, can cause imbalance within the system and result in discoordinated breathing (dyspnea). In other words, higher perceptions of throat tightness and dyspnea at rest in the E-PVFM group could point to muscle inadequacies at rest (especially outside of the larynx), amplifying aberrant muscle responses to strenuous activities.

5.6 CONCLUSION

This prospective mixed-design study was the first step in a programmatic line of work to help improve diagnostic accuracy of PVFM. Results show inspiratory and expiratory dyspnea are good perceptual correlates to E-PVFM. However, further investigation is needed to improve severity

benchmarks for pathology and to differentiate symptoms in E-PVFM from normal levels of dyspnea found with exertion. Validated severity benchmarks and cutoff scores can then be used to determine level of disability and appraise treatment outcomes. Future studies are also needed to determine perceptual differences between PVFM and other disorders with overlapping symptomology (e.g., asthma, COPD, panic disorders). These findings should be studied in relation to normal variation in exercise intolerance as a result of normal physiological limitations (e.g., deconditioning). Findings can guide diagnostic paradigms and reduce prevalence of misdiagnosis and mismanagement in the PVFM population. In addition to studying normative benchmarks for pathology using perceptual features that correlate with PVFM, physiological studies are also needed to better elucidate etiology underlying symptoms. Outcomes of this study and can help guide clinical diagnostic approaches and future academic investigations into physiological and etiological factors causing PVFM.

6.0 SYNTHESIS & FUTURE DIRECTIONS

Exercise-induced episodic laryngeal breathing disorders (E-ELBD) are thought to originate from laryngeal impedance acutely triggered by exertion (Shembel et al., 2017). Numerous symptoms and laryngeal patterns have been implicated in E-ELBD. However, whether any of these clinical presentations are *indicative* of E-ELBD up until this point have been largely unknown due to sparsity in prospective study, normative comparisons, and validated metrics. As a result, clinicians have been forced to rely heavily on expert opinion. Considering laryngeal signs and patient-reported symptoms are currently the "gold standard" to diagnose E-ELBD, the ambiguity surrounding the clinical utility of these features is concerning. Therefore, to address these knowledge gaps, the goal of the present study, described in full in the previous two manuscript chapters, was to characterize physiological and perceptual features characteristic of E-ELBD. Stress reactivity (temperament) and autonomic regulation as two potential mechanisms underlying these presentations were also explored to help identify directions for future programmatic study. The findings will be summarized and synthesized in the following section. How these findings fit into the broader picture of ELBD pathoetiology, and their implications for future investigation, will then follow.

6.1 SUMMARY & SYNTHESIS OF MANUSCRIPT CHAPTERS

Results of the study showed statistically significant group (E-ELBD, control) and condition (rest, exercise) differences with glottal configuration and dyspnea. Specifically, subjects with E-ELBD

reported significantly higher inspiratory and expiratory dyspnea severity levels with exercise than participants in the athletic control group. Symptoms of stridor and throat tightness in response to exercise were the other two most prevalent features reported in the E-ELBD group, which could mean these symptoms are more common in the exercise variant as compared to symptoms related to voice complaints (dysphonia) and airway protection (cough, dysphagia). However, severity of stridor and throat tightness varied greatly across individuals with and without E-ELBD, and group differences were not observed on these two parameters. These findings suggest these latter two features as less sensitive diagnostic indicators of ELBD and may be more common in athletes, in general.

Participants in the E-ELBD group also presented with paradoxical inspiratory adduction and blunted expiratory abduction (and at times paradoxical expiratory adduction) in response to strenuous exercise. These laryngeal patterns directly contrasted with increased vocal fold angles (glottal widening) in response to exercise seen in healthy athletic volunteers, during both inspiratory and expiratory cycles. Arytenoid prolapse was seen variably in both athletic groups, while epiglottic collapse and ventricular compression were rarely seen in either group, suggesting the former two features are more prevalent in athletes in general. Finally, trends in autonomic parameters showed smaller sympathetic responses or sluggish parasympathetic deactivation during strenuous exercise (in the context of seemingly alarming E-ELBD attacks thought to trigger "fight or flight" sympathetic responses) and slightly greater parasympathetic reactivation after exercise in the E-ELBD group, compared to the control group. However, no significant differences were found in sympathovagal biomarkers. Trends in group differences was in contrast to similarities between groups on the EATQ-R Fear subscale, suggesting similar stress reactivity between the two athletic groups.

In summary, the following features appear to be good diagnostic indicators of the exercise-induced variant of E-ELBD, and especially when seen in combination, will improve diagnostic specificity:

(1) Paradoxical inspiratory glottal movement with exertion

(2) Inspiratory and expiratory dyspnea under exertion

The following thresholds can be used to increase confidence in the diagnosis of E-ELBD: greater than (a) an 8° decrease in anterior glottal angle indicative of inspiratory vocal fold adduction during strenuous exercise, compared to at rest baseline laryngoscopy, (b) less than 32° true vocal fold adduction during expiration with exercise, compared to rest, suggesting a blunted expiratory vocal fold response, (c) 30/100 or greater on the VAS with strenuous exercise, and (d) 20/40 or more on the Dyspnea Index. Additional investigations comparing the presence and severity of these clinical features with other breathing disorders (e.g., asthma, panic disorders) should also be conducted. These comparative studies will further define ELBD characteristics and distinguish features of ELBD from other conditions with similar signs and symptoms. Replication studies with larger sample sizes are also needed to determine how the following clinical presentations, present in the E-ELBD group, but shown to vary with athletes of comparable athletic abilities and age, fit into the ELBD spectrum:

(1) Laryngeal patterns consisting of blunted expiratory glottal abduction (or at times paradoxical adduction) with exertion

(2) Arytenoid prolapse with exertion

(3) Throat tightness with exertion

(4) Stridor with exertion

(5) Systolic blood pressure at maximum exertion

(5) Heart rate recovery post-maximum exertion.

A few key points should be emphasized. First, laryngeal pattern differences between the two athletic groups were *only* appreciated during the exercise challenge, demonstrating the need to observe laryngeal kinematic patterns *concurrently* with provocation. The indistinguishable group differences in glottal patterns seen during quiet, vegetative breathing at baseline (rest), stark contrasts in laryngeal patterns between groups with exercise, and the quick resolution of aberrant responses post-exercise in the experimental group, all point to the clinical utility and even imperative of incorporating provocation challenge into standard of care assessment protocols for patients with suspected E-ELBD.

Along the same lines, similarities in arytenoid response to rigorous exercise between the two groups of adolescent athletes not only demonstrates the relevance of provocation challenge, but also illustrates the importance of normative comparisons. Previous literature has suggested the presence of arytenoid prolapse points to E-ELBD, citing reduced muscle tone, tissue redundancy, and smaller airway diameters as potential underlying causes (Bent et al., 1996; Christopher & Morris, 2010; Nagai et al., 1992; Pinho, Tsuji, Sennes, & Menezes, 1997; Hudgins, Siegel, Jacobs, & Abramowsky, 1997). However, these laryngeal characteristics outside the ELBD literature have also been reported to be features of normal laryngeal development and may not be unique to patients with E-ELBD (Fitch & Giedd, 1999; Sapienza, Ruddy, & Baker, 2004; Hirano 1983). When floppy laryngeal tissue or cartilages are present in combination with high negative inspiratory pressures (e.g., during physical exertion), the laryngeal tissue can get "sucked in" to the glottal lumen, resulting in airway obstruction (Christopher & Morris, 2010). Because typical adolescent athletes in the context of ELBD typically do not undergo continuous laryngoscopy exercise challenges, it is not surprising these same supraglottic responses have not been previously

acknowledged in the ELBD literature. These findings highlight the importance of normative references when attributing clinical features to pathology.

The take home point may be that arytenoid prolapse can occur variably in young athletes, in general, and may not necessarily *indicate* E-ELBD. However, additional investigation is needed to confirm or refute this assertion. Similarly, the prevalence and severity of "twitchy" laryngeal responses and laryngeal edema/erythema, both features that have been attributed to ELBD, were equally prevalent in the two athletic groups. Again, these findings emphasize the need for caution when attributing laryngeal findings to ELBD in absence of normative reference points.

In a similar vein, stress reactivity (temperament) may not have as prominent a role in ELBD pathogenesis as previously alleged (at least not in the exercise-induced variant). Results on the Fear subscale of the EATQ-R showed athletic groups were similar in their self-perceived reactions to anticipated stressful events. These similarities contrasted with significantly lower normative scores across the general adolescent population on the same subscale in a previous study (Muris & Meesters, 2009). Because this is the first study on ELBD and temperament that included a typical athletic group of comparable age, gender, and athleticism, it is not surprising that stress reactivity could likely have been previously overgeneralized to athletes with ELBD. This is not to say psychological stressors have no influence in E-ELBD pathogenesis. However, what may differ between athletic groups with and without E-ELBD is not their temperament, but their *physical* responses to stressors. Potential future directions addressing the study of physical stressor responses will be discussed in greater details in Section 6.3.

Trends in autonomic responses between the two groups could also point to differences in how the system responds to physical stressors in athletes with and without E-ELBD. Trends in decreased sympathetic output (i.e., decreased parasympathetic withdrawal) during heavy exertion

and faster parasympathetic reactivity after exercise seen in the E-ELBD group compared to the athletic control group align with previous studies showing robust correlations between increased parasympathetic and laryngeal muscle responses to acute stressors in healthy individuals (Helou et al., 2013, 2014). The difference between the present study and previous studies may lie in the ability to *adapt* to physical stressors, including exercise training. Typically, when a novel stressor is presented to the system, sympathovagal response is high and may persist even after the stressor is withdrawn (McEwen, 1998, 2000). With repeated exposures, however, the body adapts and sympathovagal responses become less robust and not as prolonged. However, with autonomic dysregulation, the system may not be able to acclimate to repeated athletic exposure. As a result, sympathetic "fight or flight" response may continue to be too high or prolonged. Conversely, the inability of the system to adapt may result in blunted sympatho-excitation to exercise (McEwen, 2000, 2007). The latter response may point to the lower blood pressures and slightly faster heart rate recovery outcomes seen in the E-ELBD group. These patterns have been demonstrated with physical stressors (e.g., muscle overload and fatigue) and certain types of overtraining syndromes (e.g., Addison-type) (Lehmann et al., 1998). Implications are described in more detail in Section 6.3.

6.2 STUDY LIMITATIONS

The following study limitations can provide springboards for future investigations. The first limitation was that the EATQ-R assessed the *perception* of anticipated stressful events in athletes, but did not measure direct physical responses to psychological stressors. Previous studies have shown psychological stressors can have negative physical effects on the body (e.g., hormonal,

musculoskeletal), resulting in decrements to athletic performance (Kreher & Schwartz, 2012). Therefore, future investigation should address physiological stress responses to provocation challenge, as well as psychological appraisal of the event, to more fully appreciate the role (or lack thereof) of psychological factors in E-ELBD and the pathways through which they might mediate physical responses. For example, the type of event (e.g., important competition), appraisal of the stressor (e.g., benefit or harm), and coping mechanisms used to mitigate stress responses (e.g., problem- versus emotion-focused) could all play roles in physical stress responses in E-ELBD (Baker, Côté, & Hawes, 2000).

The second limitation of the study was the omission of tidal volume measurements. As a result, influences of respiratory physiology on laryngeal muscle responses could not be directly assessed. The decision to forgo assessment of this parameter was twofold. From a theoretical perspective, the primary goal was to identify symptoms and laryngeal patterns that represent E-ELBD to more accurately diagnose patients in clinical settings as well as to better identify inclusionary criteria for future studies. Having a better appreciation for the composition of E-ELBD presentation with the present study's findings, the next step is to assess the role of the pulmonary system in laryngeal-respiratory system coupling in future studies. From a methodological perspective, inductance plethysmography, used to estimate tidal volume and other pulmonary parameters, would have interfered with the placement of the heart rate monitor to obtain HRR calculations in the present study.

The third limitation was the use of the exertion scale to determine levels of physical exertion. Although previous studies have shown exertion scales, such as the Borg Scale, to be a good indicator of exertion, it can be influenced by mood and other psychological factors affecting appraisal of the event. More objective measures, such as cycle trainer RPM or resistance (watts),

would have addressed these concerns. Fortunately, both groups reported similar severities in leg fatigue with the exercise challenge, and duration to maximum exertion was comparable between groups. These findings suggest physical efforts during exercise challenge, as well as the appraisal of physical effort, were similar across the two groups, and places confidence in the physical exertion scale as a good indicator of exertion for present purposes.

A fourth limitation surrounds alternate theories for autonomic parameter (HRR, SBP) differences found between the two athletic groups. Slightly faster HRR seen in the experimental group post-maximum exertion could be attributed to the rescue breathing techniques (e.g., pursed lip breathing) the majority of participants needed to implement to alleviate ELBD attacks induced by provocation challenge. Previous studies found that increased airway resistance during pranayama yoga breathing increases parasympathetic response as a way to "soothe" the body (Streeter et al., 2012). However, there is a limitation to extrapolating these previous findings to the present study as the ujjayi breath or "ocean sound" in yoga involves pharyngeal constriction configurations that differ from oropharyngeal configurations in traditional respiratory retraining techniques (e.g., pursed lip breathing) (Blager, 2000) (see *Appendix G: Respiratory Retraining Therapy (Conceptual)* and *Appendix H: Respiratory retraining (Mass Eye and ear Protocol)*). Therefore, whether parasympathetic responses with respiratory retraining are similar to parasympathetic responses in yoga breathing is unknown and requires further investigation. It would obviously be unethical to withhold rescue breathing techniques to mitigate ELBD attacks. One way to address both ethical and methodological concerns for future studies would be to have both groups with and without ELBD implement rescue breathing immediately after the height of maximum exertion. If differences in HRR are still seen between groups, these findings can increase confidence that parasympathetic reactivation plays a role in the autonomic balance hypothesis.

The final limitation is that asthma was not formally ruled out in participants enrolled in the athletic control group. Control participants were recruited based on their having no symptoms of dyspnea, low scores on the Dyspnea Index, and the assumption lung volumes and capacities were highly functional at such competitive levels of athletic capabilities. However, there could be a possibility, although highly unlikely, that the healthy individuals in the control group could have had lower predicted long volumes (FEV1 < 80% predicted) without any symptoms of asthma. However, if this were to be the case, it is also highly unlikely these subclinical findings would have significantly influenced participant symptom ratings or laryngeal response patterns in the present study. Previous studies have shown that the amount of laryngeal responses to lower airway pathology directly correlates with the severity of pulmonary pathology (Jamilla et al., 2000), although the exact amount of laryngeal adduction has yet to be quantified.

6.3 FUTURE DIRECTIONS

Study findings provide insight into approaches to diagnostic assessment of ELBD; specifically, what features can be used to diagnose E-ELBD and the importance of provocation challenges to improve diagnostic specificity. Study findings also provide insight into how we think about other clinical features of E-ELBD that occur variably within a broader context, how E-ELBD and other ELBD variants (e.g., irritant-inducing) fit into the overall comprehensive taxonomy framework, and the consideration of other mechanisms that can drive clinical expression in E-ELBD (and ELBD in general). Results indicate abnormal true vocal fold dynamics and sensations of dyspnea with provocation challenge to be the features that best differentiate typical from pathological clinical presentations in athletes with ELBD. However, the heterogeneity and variable presence of

other clinical features (e.g., throat tightness, arytenoid prolapse), even within a seemingly homogenous group of athletes with and without E-ELBD, points to the multifactorial nature of ELBD. Findings reaffirm that ELBD is likely not one entity, and therefore it might be wise to consider ELBD a symptom complex and not a sole diagnosis. The first section (Section 6.3.1) provides a proposed change in how we think about and diagnose ELBD. The second section (Section 6.3.2) is a summary of other potential mechanisms that could also play a role in ELBD presentation to set the tone for future studies. The third section (Section 6.3.3) is a summary of potential mechanisms involved in other trigger variants in ELBD within the comprehensive taxonomy framework (*c.f.,* Section 2.2.3) to guide future investigations.

6.3.1 Proposed (updated) approaches to ELBD diagnostics

Descriptions of how practitioners approach and diagnose ELBD (e.g., "how I do it" papers) are abundant in the ELBD literature. However, without objective assessment and normative references to assess the validity or effectiveness of these methods, clinicians are left to rely on expert opinions and unsubstantiated claims to make clinical decisions. Unfortunately, the lack of consensus in key features of ELBD and dearth of validity in quantitative methods to diagnose the spectrum of conditions results in misrepresentations of key features and inherent cognitive biases (e.g., anchoring effect[22]).

In fact, these shortcomings even presented themselves in the dissertation study. One of the participant in the E-ELBD met all inclusionary criteria for suspected ELBD *a priori*. He had

[22] The tendency to rely on one trait or piece of information when making decisions. Usually influenced by order effect.

dyspneic symptoms that were detrimental to his athletic performance, scored higher than a 10/40 on the Dyspnea Index, and presented with "abnormal" laryngeal patterns: oscillatory motion of the corniculate cartilages and true vocal folds during the baseline laryngoscopy and exercise laryngoscopy examination, respectively. Therefore, he was enrolled in the study. However, an ELBD episode could not be provoked during the exercise challenge despite vigorous pedaling on the bike with extreme resistive loads for three consecutive minutes. Consequently, per the study's protocol, his laryngoscopic examinations were removed from analysis. The decision was made to analyze the other parameters based on (at that time) current knowledge of ELBD presentation informed by a comprehensive framework from previous literature (Shembel et al., 2017).

Retrospectively, knowing that individuals with and without ELBD can present variably with "twitchy" larynges, the individual would not have been included into the study's experimental group (of note, post-hoc analysis without these data points showed greater differences between groups on dyspnea severity during exercise, but did not change the story surrounding high variability across the other common auxiliary features or in cardiovascular and temperament findings). There is a chance this individual may have had another condition (e.g., mitochondrial dysfunction) but was instead given a diagnosis of ELBD, based on informed knowledge of ELBD features at point in time. Regrettably, the participant was lost to clinical follow up, as is often the case with individuals who find little relief with traditional respiratory retraining methods for ELBD. Results of the dissertation study suggest we might be misattributing laryngeal patterns, especially at rest, to ELBD, resulting in the over-diagnosis of the condition. Ironically, this is the very frustration healthcare professionals have had with the high rate of misdiagnosis of other conditions in the ELBD population. Unfortunately, where ELBD was once the "zebra among

horses" in specialty voice clinics, we could very likely now see any horse with black and white coloring as zebras.[23]

In general, how we approach ELBD diagnostics needs to be reconsidered. One way to restructure diagnostic paradigms can be extrapolated from clinical approaches to the diagnosis and management of dysphagia, another symptom complex with many potential underlying mechanisms driving clinical expression. Specifically, it is not enough to affirm the presence of dysphagia. Clinicians must also consider where the dysfunction is occurring within the head and neck and what is causing the dysfunctional deglutition. That is because mechanisms underlying difficulty swallowing will drive how we provide clinical care. For example, the management of someone with dysphagia caused by Amyotrophic Lateral Sclerosis (ALS, also known as Lou Gehrig's disease) will be different from that of someone with dysphagia due to a Zenker's diverticulum, general deconditioning, or esophageal cancer. The same should hold true for ELBD. Unfortunately, typical assessment methods in ELBD involve confirmation of ELBD through symptom reporting without asking what causes these presentations or *why* these presentations occur in the first place. Diagnostic approaches commonly rely on self-reported patient symptom history and forgo direct visualization or provocation of laryngeal responses, making it further challenging to determine the cause or locus of dysfunction. As a result, we are left with management using blanket approaches irrespective of etiology (e.g., pursed lip breathing, see

[23] Interestingly, the clinical utility of provocation continues to be debated amongst experts, the most recent of which occurred during the Fall Voice Conference webinar on September 26, 2017: "Paradoxical Voce Fold Dysfunction: Philosophy and Management" (panelists: Mary Sandage, PhD CCC-SLP; Adrianna Shembel, M.A. CCC-SLP; Laura Matrka, MD; Albert Merati, MD; and Milan Amin, MD). During this webinar, the need for provocation was challenged on the notion the diagnosis and course of treatment would not differ (*c.f.*, Section 2.1.2 for pros and cons of provocation challenge)

Appendix G: Respiratory Retraining Therapy (Conceptual)). It is therefore not shocking that only two-thirds of the ELBD population report resolution of their symptoms (De Guzman et al., 2014).

Just as the penetration-aspiration scale[24] in the domain of dysphagia can be used to evaluate loci and severity of dysphagia (Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996), identifying and quantifying glottal angles and supraglottic configuration can be used to determine the location of obstruction and the severity of ELBD. Different anatomical, physiological, and symptom-based patterns can not only provide insight into the cause but can also be used to guide how we treat patients. Along the same lines, without direct visualization using swallow function tests (e.g., modified barium swallow examinations [MBS], fiberoptic endoscopic evaluation of swallowing [FEES]), in conjunction with functional assessment (e.g., bolus trials with different food and liquid consistencies), there is no way to determine why or where within the system the dysfunction is occurring. A bedside swallow, although a great screening tool, should not be used to diagnose dysphagia any more than a case history and patient-reported symptoms should be used to diagnose ELBD, especially when better diagnostic approaches exist and have good clinical utility. Furthermore, functional assessment using typical provocations that elicit the ELBD episode serve the same purpose as in the evaluation of swallowing with consistencies that closely represent foods consumed during regular mealtimes. The more clinicians can provide functional assessments mimicking natural settings and situations, the better the specificity of the diagnostic approach. Table 6-1 compares proposed gold standard assessment methods in ELBD diagnostics with current gold standard methods for diagnosing dysphagia.

[24] The penetration-aspiration scale is an 8-point interval scale describing how far material enters the airway with deglutition during a Modified Barium Swallow (MBS); the scale also addresses whether material is expelled out of the airway if it does, in fact, enter the airway (i.e., if the individual is sensate).

Table 6-1. Similarities Between ELBD and Dysphagia Diagnostic Methods

Assessment Method	ELBD	Dysphagia
Screening tool	Case history, Dyspnea Index, Symptom-reporting	Case history, Bedside swallow examination
Diagnostic test	Continuous laryngoscopy	Modified barium swallow, videofluoroscopy
Functional component	Provocation challenge (exercise, irritants)	Barium trials with different consistencies (nectar, thin)
Quantifiable severity benchmarks	Dyspnea severity (VAS), Anterior glottal angle measures, Supraglottic 0-3 rating scale	Penetration-Aspiration Scale, Quantitative measures of pharyngeal transit time, hyoid displacement, and timing of laryngeal vestibule closure relative to bolus arrival
Examples of anatomical deficits (obstruction) attributing to disorder's symptom complex	Vocal fold lesions, laryngomalacia	Zenker's diverticulum, esophageal web
Examples of associated pathology contributing to disorder's symptom complex	Asthma, gastroesophageal reflux disease	Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS), Cerebrovascular accident (CVA)

6.3.2 Other potential E-ELBD mechanisms

As mentioned previously, there are likely different mechanisms that can underlie signs and symptoms in ELBD. The differences in laryngeal patterns, symptom presentations, and wide range

of symptom onset and resolution of symptoms[25] speaks to these likely differences in mechanisms (or differences in discoordinated patterns for laryngeal-pulmonary coupling) driving clinical expression. Several of these mechanisms—musculoskeletal dysfunction, somatosensory integration issues, and abnormal respiratory physiology—will be addressed in the following sections.

6.3.2.1 Musculoskeletal Dysfunction

One alternative mechanism may involve fatigue or discoordination of muscles within the respiratory system. Although primary respiratory muscles are typically fatigue resistant, how energy is supplied and stored within the muscles and how muscles respond to activities involving increased loads of excessive strength or endurance (tension and contractibility) can influence the fatigability of respiratory muscles. Fatigue and discoordination can also be influenced by central respiratory drive or neuromuscular transmission (Aldrich, 1988; Macklem & Roussos, 1977). Studies have shown that respiratory muscle efficiency and proclivity towards inspiratory muscle fatigue has more to do with the relationship between energy demands and supplies than the percentage of fatigue-resistant fibers in the inspiratory muscles. Respiratory muscle efficiency can be further reduced by lung hyperinflation or how the intercostals and accessory muscles are recruited in respiration. Lower cardiac output may also decrease the rate at which energy is supplied to the respiratory muscles (Macklem, Cohen, Zagelbaum, & Roussos, 1981). This latter point is especially interesting considering trends in lower systolic blood pressures were found in the ELBD group in the dissertation study.[26] Finally, layering muscle contractions for high intensity

[25] Range of reported symptom resolution in dissertation study: 15 minutes – 2 hours

[26]Although SBP readings were, on average, lower in the E-ELBD group, average diastolic blood pressures (DBP) rose slightly with exercise in the E-ELBD group. Typically, DBP will remain the same or become lower in athletes with

exercise, especially when other muscle groups are involved in muscle contraction for throwing or kicking a ball may lead to earlier blood lactate accumulation, increased ventilation, and faster fatigue (McArdle et al., 2010).[27]

With such a seemingly simple task as breathing, it is easy to forget that the muscles of respiration play a vital role in respiratory modulation, especially in the context of ELBD. For instance, the primary muscles of inspiration—the diaphragm and the posterior cricoarytenoid (PCA) intrinsic laryngeal muscle—facilitate lung inflation and increase airway patency, respectively, during both rest and exercise (Hillel, 2001; Hlastala & Berger, 2001; Jones, Harvey, Marston, & O'Connell, 2013). With certain aerobic activities such as distance running, the abdominal muscles and external intercostals may also activate to optimize oxygen-carbon dioxide exchange by preventing the lungs from recoiling too quickly during expiration (Zemlin, 1998) or in sprinting to maximize airflow for high ventilatory demands.

Because breathing is constant for metabolic respiration, the respiratory muscles cannot ever fully deactivate or the system goes into respiratory distress. This is especially true for inspiratory muscles because inspiration is always active (except with mechanical ventilation). Fatigued muscles have more trouble firing within their (typically) invariant patterns of timing for appropriate patterns of muscle activation. These atypical patterns result in detriments to respiratory muscle coordination needed to maintain the body's internal milieu. Additionally, the use of inhaled corticosteroids has been shown to inhibit protein synthesis necessary for muscle recovery, further amplifying muscle wasting and fatigue (Dekhuijzen et al., 1996; Reid & MacGowan, 1998;

---

efficient cardiovascular systems during intense exercise. These findings, although not significant, should be considered further in future studies.

[27] Interestingly, women have been shown to have 5-10% less hemoglobin than men, which can play a role in reducing aerobic capabilities. These patterns could explain the higher prevalence of ELBD found in females (McArdle et al., 2010).

Weiner, Azgad, & Weiner, 1993). Pharmacological consequences are especially problematic in young athletes growing rapidly and undergoing frequent developmental and pubertal changes. Unfortunately, corticosteroid use is common in the E-ELBD population because many athletes are initially treated for exercise-induced asthma. Even after a correct diagnosis of E-ELBD has been made, there is typically some hesitation to completely wean from corticosteroids in fear of detriments to athletic performance from the weaning process. The high prevalence of corticosteroid use in adolescent athletes with ELBD could help explain why the condition can perpetuate in this population.

Respiratory muscle fatigue or discoordination can become amplified with additional physical demands, especially when these muscle groups are already pre-fatigued from previous physical loads or when there has not been enough time to recover. In fact, prolonged periods of chronic musculoskeletal overload to the system without rest can result in overtraining syndrome[28] (Zając, Chalimoniuk, Maszczyk, Gołaś, & Lngfort, 2015). Overtraining syndrome comes in two variants, sympathetic and parasympathetic, both of which can occur when the system is unable to maintain responses to allostatic loads (McEwen, 2000). Studies have shown that parasympathetic overtraining syndrome, more common in aerobic sports, can lead to lower resting heart rates, lower baseline blood pressures, and blunted cardiovascular response to exercise, as the body places itself into persistent "rest and digest" mode in an attempt to repair itself (Kreher & Schwartz, 2012). Trends in smaller blood pressure responses to exercise and higher parasympathetic responses post-maximum exertion seen in the experimental group with HRR could point to overtraining syndrome as an alternative underlying mechanism in E-ELBD.

[28]Also known as burnout, staleness, failure adaptation, under-recovery, training stress syndrome, chronic fatigue, and unexplained underperformance syndrome (Kreher & Schwartz, 2012).

To prevent respiratory muscle fatigue or discoordination caused by high intensity or prolonged aerobic activity (e.g., sprinting, long distance running, respectively), small, stepwise increases in training intensity and frequency are required. These adaptive increases have been termed "functional overreaching" (Kreher & Schwartz, 2012). Conversely, increases in workload that are too fast or too long can cause prolonged muscle fatigue (referred to as "nonfunctional overreaching"), making the muscles susceptible to further discoordination and even injury. Muscles also need appropriate intervals of rest interspersed across these workload increases to be able to recover from the physical stress that comes with training. Numerous increases in training loads without adequate recovery lead to accelerated time to fatigue, more chronic fatigue, and decrements to athletic performance, requiring even longer periods of rest to recover (Kreher & Schwartz, 2012; Romer & Polkey, 2008; Zając et al., 2015).

Both groups in the dissertation study reported being equally active (5-7 days a week; average 1.5-hour sessions) and the average intensity *within* sessions was comparable between groups (7.5-8 on 1-10 scale). If there is validity in the parasympathetic overtraining hypothesis, the differences in autonomic outcomes between groups may lie in the stepwise intensity from one training session to the next, especially in how patients ramp-up their athletic abilities at the start of the athletic season. Conversely, these differences could be due to an inability to recover between sessions, either as a result of autonomic dysregulation, muscle weakness (e.g., inadequate energy supply or neurotransmission signals to the muscle) in certain respiratory muscle groups, or genetics. If these hypotheses hold true, future treatment paradigms for patients with E-ELBD may need to focus on the intensity of load increments from one session to the next. For example, mileage may need to be ramped up more slowly for runners with ELBD. Or the patient may need to implement more active rest days in between training sessions (i.e., anaerobic cross-training

using different muscle groups) to give certain respiratory muscle groups a rest without losing too much in the way of athletic abilities.

A third hypothesis could point to inadequacies in muscle pattern recruitment of the primary respiratory muscles, resulting in faster activation of fatigue-prone secondary respiratory muscles or discoordination between muscle groups. Previous studies have shown accessory muscles of the head and neck are recruited when lower respiratory system muscles are weakened or fatigued. For example, the scalenes and sternocleidomastoid (SCM) elevate the ribcage to keep the lungs from deflating when the diaphragm is tired/weak; the genioglossus and geniohyoid prevent upper airway collapse with intercostal muscle inadequacy (Brouillette & Thach, 1979, 1980). However, because the accessory muscles are better suited for quick-burst activities, such as cough and deglutition, when they are recruited for activities requiring intense or prolonged training, they fatigue more quickly than other muscles of respiration.

Already pre-fatigued respiratory muscles may also explain abnormal laryngeal patterns in the context of athletic activity. With greater number of muscles recruited comes higher ventilatory demands and much more coordination required across muscle groups for optimal respiration. Specifically, with vigorous exertion, the serratus posterior superior raises the upper ribs, while the serratus posterior inferior pulls down on the lower ribs. The levatores costarum raises the rib below each costarum muscle, often in conjunction with contraction of the iliocostalis (thoracis and cervicis) to elevate the rib cage. Finally, the quadratus lumborum increases the vertical height of the thorax by lowering the twelfth rib (Gray, 2009; Spiro, Silvestri, & Agusti, 2012). With forced expiration during anaerobic workloads (e.g., sprinting), the internal intercostals, transverse thoracis, transervse abdominus, rectus abdominus, external obliques, and internal obliques activate to push the diaphragm upwards and pull the ribcage downwards to maximum ventilatory effort in

the lungs (Hlastala & Berger, 2001). These muscle groups also need to coordinate with each other as well as with the other primary muscles of respiration, mentioned previously. The athletic synchronous "dance" required of these various muscles during high physical demands is in stark contrast to the number of muscles involved in quiet, vegetative breathing that need to synchronize with each other.

Unfortunately, overuse of these respiratory muscle groups from heavy athletic demands can result in muscle fatigue (e.g., low energy reserves) and discoordination, leading to decreases in airway patency and stability. The larynx has been shown to compensate for inadequacies in expiratory abdominal muscle recruitment in a phenomenon known as positive end-expiratory pressure, or auto-PEEP. The larynx in auto-PEEP reduces upper airway diameter by adducting the vocal folds on expiration, "braking" air flow to slow lung emptying, thereby reducing tachypnea (fast and shallow breathing) and breath stacking (successive inspiration prior to full expiration of the previous breath). Auto-PEEP patterns have been shown to minimize respiratory muscle load to prevent further muscle fatigue and decrease hyperventilation (Brancatisano, Dodd, & Engel, 1984; Jamilla et al., 2000).[29]

The laryngeal patterns characteristic in auto-PEEP could explain the blunted expiratory vocal fold abduction responses seen in patients with E-ELBD, compared to controls, during strenuous exertion. If these patterns are representative of auto-PEEP, the abductory vocal fold responses seen with expiration in the experimental group could actually be a compensatory attempt to reduce the effects of lower respiratory muscle dysfunction. If this is the case, treatment

[29]Interestingly, individuals who exhibit these auto-PEEP patterns can also have changes to lung volume and intrathoracic pressures which can decrease cardiac output (systolic blood pressure) without changing heart rate (Luecke & Pelosi, 2005). The role of laryngeal patterns involved in auto-PEEP should be considered further in the context of the lower systolic blood pressures readings and relatively unchanged raw heart rate readings seen during intense exercise in the E-ELBD group, compared to the athletic control group, in the present study.

paradigms should focus on increasing the strength or endurance of the instigating muscles of respiration causing the discoordination or dysfunction and not directly on laryngeal responses (the traditional approach to ELBD).

In addition to expiratory laryngeal compensation, the larynx may also compensate during inspiration. The thyroarytenoid (TA) and cricothyroid (CT) intrinsic laryngeal muscles can stiffen and elongate the vocal folds, respectively, to reduce airway collapse and prevent the vocal folds tissue from "fluttering" and getting "sucked" into the glottal lumen (Christopher & Morris, 2010). In the present study, vocal fold stiffening and elongation were seen in 6/13 (46%) of individuals with E-ELBD and in 6/14 (43%) of individuals in the control group during vigorous exercise. The larynx's inability to prevent tissue collapse may be due to difficulties compensating for lower respiratory tract muscle insufficiency. Further investigation is needed to not only determine the merit of this theory but to also evaluate whether TA/CT compensation plays a role in perceived severity of symptoms (dyspnea, stridor, throat tightness) in patients with E-ELBD.

Interestingly, the traditional approach to ELBD management—respiratory retraining therapy—is thought to compensate for reduced airway patency when laryngeal obstruction occurs. Decreasing the configuration of the oropharynx in pursed lip rescue breathing, for example, may work similarly to auto-PEEP, resulting in elongation of the expiratory phase and maintenance of ventilation at appropriate lung volumes (Fallon, 2004). However, these traditional breathing strategies have been shown to work in only two-thirds of individuals with E-ELBD (De Guzman et al., 2014). More recent studies showing improvements in athletic performance after inspiratory and expiratory muscle strength training in both healthy and disordered athletic populations points to respiratory system muscle weakness as another potential underlying mechanism in some patients with E-ELBD (McConnell & Romer, 2004; Romer, McConnell, & Jones, 2002; Romer &

Polkey, 2008; Witt, Guenette, Rupert, McKenzie, & Sheel, 2007). However, more empirical evidence is needed to determine the role the musculoskeletal system and strength training plays in E-ELBD.

To summarize, the larynx is typically implicated in the symptoms patients with ELBD experience. However, these sensations could also stem from other accessory muscles of the neck, base of tongue, or oropharynx used in respiration. If the accessory muscles are being inappropriately recruited for respiration during high physical demands, they can become fatigued. This mechanism could explain the (on average) higher perceptual levels of dyspnea and throat tightness reported in the ELBD group at rest, even with seemingly normal laryngeal kinematics during the same period. Anecdotally, the majority of individuals with E-ELBD exhibited some form of tension in the head neck musculature on digital palpation. Common muscle groups included the base of tongue and sternocleidomastoid muscle. Future study is needed to determine the role accessory muscle tension and respiratory discoordination/fatigue has on ELBD.

6.3.2.2 Somatosensory Dysfunction

Previous studies have shown that muscle fatigue and tension can distort somatosensory information coming from muscles. Typically, sensory information coming from mechanoreceptors—types of afferent receptors that detect stretch, pressure, and temperature within the muscle—trigger reflexive responses within the airways. Two types of afferent pulmonary stretch receptors, slowly adapting (SARs) and rapidly adapting (RARs) work closely with the vagus nerve to regulate sensory inputs. The SARs sense changes in lung volume and respond to changes in muscle tone and mechanical distortion in the airways to prevent excessive stretching of the lungs during inspiration. When SARs are activated, they send signals through the vagus nerve to the inspiratory area of the medulla and pneumotaxic area in the pons, initiating the

Hering-Breuer reflex to terminate inspiration and initiate expiration as to not over-inflate the lungs. The Hering-Breuer reflex may also play a role in the initiation of inspiration with sensation of lung under-inflation (Barnes, 1996; Dempsey & Pack, 1995; Hlastala & Berger, 2001; Karlsson, 1994; Middlekauff, Park, & Moheimani, 2014).

Conversely, the pre-Bötzinger complex, which initiates inspiration through bulbospinal pathways to motoneurons of the inspiratory muscles, activates the diaphragm (Butler, 2007; Levitzky, 1995). Another area in the medullary respiratory center, rostral to the pre-Bötzinger complex, is active in expiration involving increased respiratory drive. The two areas, the pre-Bötzinger complex and the area rostral to the pre-Bötzinger complex, are collectively known as the ventral respiratory group, and work together to maintain rhythmic respiration (Butler, 2007). Medullary activity involving the vagal and diaphragmatic afferents appear to be more active with expiratory load changes, playing a role in ribcage and ventilatory response coordination (Barrière, Delpierre, Del Volgo, & Jammes, 1993; Gozal et al., 1996). The brainstem also controls a variety of other laryngeal sensorimotor processes vital for regulating and protecting the respiratory system (e.g., cough, swallowing, expiratory, apneic, and diving reflexes) (Arteaga-Solis et al., 2013; Dempsey & Pack, 1995; Mukhopadhyay et al., 2007).

Sensory signals from the larynx have also been traced from the vagus nerve to the mesocortex, an area of the brain thought to be responsible for hypercapnic sensations, via the medullary ventral and dorsal respiratory nuclei. Additionally, limbic system activity in the amygdala has been shown to activate in conjunction with the vagus during resistive inspiratory load and to decrease during resistive expiratory load (Gozal et al., 1996; Macey et al., 2003; Von Leupoldt, Mertz, Kegat, Burmester, & Dahme, 2006). These findings support the notion that the vagus is involved in both sensory and affective processing of dyspnea (Thach & Bradley, 1997).

Chronic or prolonged mechanical stimuli within the larynx has been shown alter receptor responses and can even cause neuroplastic changes in the brainstem and limbic system. Changes in laryngeal vagal reflex response thresholds can cause a cascade effect of increased sensitivity to additional stimuli over time, resulting in muscle tension or spasms upon exposure even to typical sensory stimulation (Morrison et al., 1999). A defective inspiratory termination threshold or neoplastic changes within these areas of the brain could explain some of the clinical presentations seen in E-ELBD. Signals to and from the vagus nerve and bulbar regions may be affected in this population, resulting in early inspiratory termination before metabolic needs of the system are met. Specifically, these mechanisms may help explain the atypical adductory responses of the vocal folds seen during the inspiratory phase in conjunction with increased physical demands; it may also help explain the sensation of dyspnea patients with E-ELBD experience.

A study by Hammer and Krueger showed mechanical sensory receptor thresholds in the larynx were lower in female compared to male subjects. The investigators attributed these findings to increased sensory laryngeal nerve firing in women and indicated results may explain the higher prevalence of functional[30] voice disorders and other sensorimotor laryngeal conditions seen in women (Hammer & Krueger, 2013). If this theory holds true, it might also help explain the 2:1 female-to-male ratio seen in the E-ELBD group in the present study. However, this theory does not explain why some female athletes develop ELBD while other female athletes do not. Comparative studies involving mechano-sensory manipulation in participants with and without ELBD as well as between the sexes are needed to better identify the role these response patterns play in ELBD pathogenesis.

[30] Physiologically-based, not psychologically-based (as the latter is often eluded).

Previous studies have also shown there are more sensory receptors in the accessory muscles than in other respiratory muscles, which can heighten sensations of dyspnea and throat tightness when these muscles are prematurely recruited, such as could be the case with ELBD, described previously in the musculoskeletal section (Harms, Wetter, Croix, Pegelow, & Dempsey, 2000). Additionally, the vagus nerve (CN X) innervating the larynx is in close proximity to, and overlaps with, other sensory nerves including the glosopharyngeas nerve (CN IX)—which innervates the mucosa of the pharynx, and the trigeminal nerve (CN V) and facial nerve (CN VII)—both which innervate the nasopharynx (Wilson-Pauwels, Akesson, & Stewart, 2002). This overlap explains why sensations within the pharynx are hard to define and why individuals with nasopharyngeal inflammation may complain of a sore throat (Eccles, 2003). It can also explain sensations of throat tightness and dyspnea at rest experienced in the E-ELBD group, even in the presence of normal laryngeal dynamics.

Future studies involving manipulation of various mechanical sensitivity response thresholds with simultaneous brain imaging in participants with and without ELBD are needed to determine the merit of somatosensory integration as a potential mechanism underlying ELBD. Additionally, *why* these patterns are more prevalent in women, if they do in fact play a role in ELBD pathogenesis, also need to be illuminated. Brain imaging and sensory threshold testing can also be studied in the irritant-induced ELBD population, compared to normal populations, using chemo-sensitive agents such as capsaicin to identify threshold response differences (see Section 6.3.3.1 for further details on irritant-induced ELBD).

6.3.2.3 Respiratory physiology dysfunction

Respiratory physiology plays an essential role in meeting the system's respiratory demands and should therefore be considered in dysfunctional breathing, especially in the context of ELBD. With

high ventilatory demands, the pulmonary system acutely responds by increasing the movement of air in and out of the body. This response causes an increase in gas exchange between the environment and the body and plays a role in regulation of acid-base balance. Specifically, when exercise is initiated, minute ventilation increases rapidly via increased breathing frequency and tidal volume (i.e., hyperpnea). Central feedforward commands and muscle receptor feedback commands provide information to determine the right amount of ventilation required to meet the system's needs for the given task (McArdle et al., 2010). With sustained physical demands, ventilation steadily rises in an attempt to continue to meet the system's metabolic needs before ventilatory responses eventually plateau. This shift is referred to as the *ventilatory threshold* and is believed to result from lactic acid accumulation from increased hydrogen ion concentrations in the blood stream. During this period, the body needs to continue to maintain arterial gas partial pressures and pH levels to maintain homeostasis in the context of allostatic loads to the system. Increased ventilation helps eliminate carbon dioxide buildup and restores acid-base balance. The maintenance of this acid-base balance is accomplished via the transport of carbon dioxide molecules to the lungs as plasma bicarbonate (HCO_3) (McArdle et al., 2010).

Various mechanisms related to aberrant respiratory physiology have been implicated in a variety of dysfunctional breathing pattern conditions including hyperventilation from heightened sympathetic responses, inadequate inspiratory-expiratory ratios, and poor body alignment (Chaitow, Gilbert & Morrison 2014; Strauss-Blasche 2000). Breathing that is too fast and shallow (tachypnea) can cause a shift from aerobic to anaerobic respiration during high physical demands. This shift can lead to hypocapnia (i.e., reduced carbon dioxide levels in the blood) and blood alkalinity resulting in increased muscle contraction, muscle tetany and tension, chest pain, and dizziness (Chaitow, Gilbert & Morrison 2014).

Blood gas imbalances could be one underlying mechanism in ELBD. However, this potential mechanism does not explain why patients with ELBD would exhibit these patterns in the first place. Specifically, hyperventilation from heightened sympathetic nervous system responses is the most commonly cited reason (Chaitow, Gilbert & Morrison 2014). However, this is in direct contrast to the lower SBP responses seen within the ELBD group in the dissertation study. Patterns of hypocapnia and oxygen-carbon dioxide imbalances, if they are observed in ELBD, may instead be a *byproduct* of the musculoskeletal or somatosensory mechanisms mentioned in the previous two sections.

6.3.3 Potential mechanisms underlying other ELBD trigger variants

The final section is a review of two other ELBD trigger variants described in the comprehensive taxonomy framework (*c.f.,* Section 2.2.3): irritant-induced and psychosomatically-associated ELBD. Some potential future directions will also be addressed in these sections.

6.3.3.1 Potential underlying mechanisms in irritant-induced ELBD

Laryngeal hyperresponsiveness is thought to be the primary mechanism underlying irritant-induced ELBD (I-ELBD). The laryngeal hyperresponsiveness model assumes an abnormal glottal reflex response caused by inflammatory, viral, mechanical or chemical receptor influences. Morrison and colleagues hypothesize that chronic stimulation of sensory fibers within the larynx alters brainstem control of laryngeal sensory-motor processes (i.e., neuroplasticity), resulting in muscle tension or spasms upon exposure even to typical sensory stimulation (Morrison et al., 1999). However, the exact influences and their role in neuroplastic changes are largely unknown.

Laryngeal hyperresponsiveness is thought to begin with a *primer,* which decreases the laryngeal vagal reflex response threshold, and causes a cascade effect of sensitivity to additional sensory stimuli over time (i.e., *a faulty alarm system*) (CliftonSmith & Rowley, 2011; Hoyte, 2013; Jamilla et al., 2000; Kalk, Nutt, & Lingford-Hughes, 2011). There are many primer/faulty alarm system variables, as well as factors that can influence the primer-faulty alarm system relationship. For example, viral etiologies, specific receptors, or a combination of both, in the airways may be responsible for precipitating (priming) this hyperresponsive laryngeal reflex. Taramarcaz and colleagues showed epithelial inflammatory damage suggestive of neural changes with picornavirus, a variant of the "common cold," in patients with ELBD, which may predispose these patients to a hypersensitive response in the larynx (Taramarcaz, Grissell, Borgas, & Gibson, 2004).

Additionally, studies by Couto and colleagues, and Chandra and colleagues, demonstrated increased activity of TRPV1 in airway tissue with exposure to capsaicin (the active ingredient in hot peppers). TRPV1 are receptors that cause inflammatory reactions to the airways when exposed to noxious stimuli. They have also been shown to increase vascular permeability for calcium and sodium ions responsible for neural conduction, which may explain the increased vagal *motor* laryngeal reflex response to irritants (e.g., capsaicin) in the airway (Chandra, Gerber, & Holinger, 2001; Couto, de Diego, Perpiñi, Delgado, & Moreira, 2013; Morris et al., 1999, p. 199).

Efferent vagal motor response has also been associated with increased muscle contraction, increased breathing rate, and decreased breathing depth, which may explain why individuals with I-ELBD experience episodic dyspnea even with mild laryngeal obstruction (Fontana & Lavorini, 2006; Gimenez & Zafra, 2011; Ibrahim et al., 2007; Reidenbach, 1998; Taramarcaz et al., 2004). Chemoreceptors and mechanoreceptor expression within the larynx are also thought to change their response threshold over time with consistent stimulation, resulting in laryngeal sensitivity to

non-specific irritants (e.g., smoke, fumes, post nasal drip (PND), and acid reflux) even in the absence of the initial insult or inflammation in the airways (Couto et al., 2013; Thach & Bradley, 1997; Undem & Potenzieri, 2012; Vertigan et al., 2013). Neuroplastic changes resulting in vagally-mediated laryngospasms and apneas secondary to overstimulation of chemoreceptors in the airways have been demonstrated in canine models and infants with exposure to gastric secretions of pH levels less than 2.5 (Orenstein, 2001; Thach & Bradley, 1997).

Afferent nerves in the respiratory system have been shown to not only stimulate an efferent response to chronic irritation, but can also stimulate a local *immune* response by recruiting local proinflammatory factors (e.g., cytokines). This immune response—referred to as *neurogenic inflammation*—causes inflammation and can result in airway remodeling at the peripheral level over time (Barnes, 2001; Weigand & Undem, 2012). Studies have shown increases in subepithelial edema and antigens in laryngeal tissue of infants with arytenoid prolapse and laryngomalacia, but the exact correlation between these aberrant laryngeal patterns and immune responses is unclear (Ayres & Mansur, 2011; Chandra et al., 2001). Neurogenic inflammation has also been implicated in chronic bronchoconstriction and increased mucus production in patients with asthma (Michoud, 2005; Middlekauff et al., 2014; Taramarcaz et al., 2004; Weigand & Undem, 2012).

The laryngeal hyperresponsiveness model has its merits for I-ELBD, as evidenced by the multiple studies within various bodies of literature suggesting a neurogenic reflex and inflammatory response to irritants and various direct laryngeal stimuli. However, the model falls short in several aspects. First, the laryngeal vagal reflex response has not been directly studied in patients with I-ELBD, and should not be considered causal until directly examined. Second, inflammation of the larynx is not always appreciated on laryngeal examination in patients with the I-ELBD variant. Third, neurogenic vagal reflexes from the brainstem are not the only central

nervous system mediators that act on the larynx in respiration. The larynx also receives input from higher brain centers, where maladaptive or inappropriate laryngeal activity may be the result of the individual's *perception* of a hyper-excitable larynx.

Van den Bergh and colleagues proposed I-ELBD may have more to do with a Pavlovian-like conditioned response or affective-motivational influences than with direct neuroplastic reflexive changes in the central or peripheral nervous system (Van den Bergh, Van Diest, Dupont, & Davenport, 2012). Put differently, neural connections do much more than "sense" respiratory sensation and irritation. Behavioral control and information processing mechanisms (e.g., associative experiences, perception, attention, emotional processing, and social context) are integrated with peripheral sensations. It may not be the threshold of laryngeal responsiveness itself that is to blame, but the interaction of sensations and brain-behavior mechanisms that result in increased laryngeal response (Van den Bergh et al., 2012).

Studies comparing actual threshold responses (using laryngoscopy air puff tests and brainstem reflux responses [ABR]) and the effect of emotional influences on laryngeal hyperresponsiveness (using questionnaires/batteries and neuroimaging) are needed to determine the neurological, immunological, and psychological factors that influence episodic laryngeal obstruction and resultant dyspnea in I-ELBD.[31]

6.3.3.2 Potential underlying mechanisms in psychosomatically-associated ELBD

The primary model in psychosomatically-associated ELBD (P-ELBD) is based on the assumption that psychological factors are a direct cause of P-ELBD, or that P-ELBD, in and of itself, is a psychological disorder (somatization, conversion). For example, P-ELBD have been proposed as

[31] These topics will likely be addressed in the candidate's postdoctoral work within the next couple of years.

a need for the body to protect itself, to avoid confrontation (primary gain), or to elicit sympathy or attention (secondary gain) (Bernstein, 2014; Downing, Braman, Fox, & Corrao, 1982; Lacy & McManis, 1994; Patterson, Schatz, & Horton, 1974; Rodenstein, Francis, & Stuanescu, 1983; Selner et al., 1987). One example of how psychosomatic influences are thought to affect P-ELBD can be found in a published case report of an adolescent female who used her larynx as a "nonverbal communication tool to express her discontent of imposed exercise" her family had apparently placed on her. Once the patient was "called out" on her behavior, paradoxical movement of the vocal folds, respiratory distress, and stridor were no longer present (Liistro, Stănescu, Dejonckere, Rodenstein, & Veriter, 1990).

Dunglison was the first to suggest P-ELBD are psychogenic in origin, when he described "hysteric croup" in a cohort of female patients (Dunglison, 1842). Since Dunglison's time, many other investigators have followed suit, using nomenclature with Freudian-underpinnings, such as "emotional laryngeal wheezing" or "factitious asthma" (Christopher et al., 1983; Gavin et al., 1998; Lacy & McManis, 1994; Mrazek, 1992; Newman et al., 1995; Wamboldt, Balkissoon, & Amerigo, 2001; Yellowlees & Kalucy, 1990). Copious examples of psychological symptoms and disorders in patients with P-ELBD can be found in case reports across various disciplines (e.g., depression, somatization, conversion, obsessive compulsiveness, adjustment issues, panic, anxiety, PTSD, social stressors, body dysmorphia, hypochondriasis, chronic pain, reflex sympathetic dystrophy, and childhood abuse, to name a few) (Freedman, Rosenberg, & Schmaling, 1991; Fritz, Fritsch, & Hagino, 1997; Gavin et al., 1998; Leo & Konakanchi, 1999; Powell et al., 2000; Selner et al., 1987). However, the causal relationship between these psychological factors and P-ELBD is currently unknown.

Investigators who consider P-ELBD a psychosomatic disorder advocate this concept based on the high prevalence of co-occurring psychiatric disorders, the dearth of organic/physiological mechanisms explaining symptoms, the common symptoms seen between P-ELBD and psychological disorders, and the noted decreases in dyspneic symptoms with cognitive/behavioral-based interventions. In a case review by Leo and Konaknachi, the authors proposed P-ELBD as a psychosomatic disorder because of the "high" rate of psychological disorders independently identified in their study cohort (conversion disorder (12%), anxiety disorder (11%), histrionic and other personality disorders (6%), family/school conflicts (4%), depression (4%), psychosomatic disorders (2%), factitious disorders (2%), and somatization disorders (1%)) (Leo & Konakanchi, 1999). However, causation does not imply correlation, and the above observations do not necessarily equate a causal relationship between P-ELBD and a psychosomatic disorder. Furthermore, prevalence of many of these psychogenic disorders appears to be the same if not higher among the general population as compared to the P-ELBD population (conversion disorder was the only disorder lower in prevalence in the general population) (*c.f.,* Table 2-4. Prevalence of Psychological Disturbances in The General Population Compared to The ELBD Population. (Carter, Briggs-Gowan, & Davis, 2004; deGruy, Columbia, & Dickinson, 1987; Gordon, 1987; Grant et al., 2004; Lichstein, 1986; Somers, Goldner, Waraich, & Hsu, 2006).

Husein and colleagues have attributed P-ELBD to "psychological conversion reaction[s]" citing no abnormal neurologic testing had been reported across the P-ELBD literature, and because P-ELBD could not be explained by "medical conditions or effects of a substance" (Husein et al., 2008). However, absence of evidence is not evidence of absence. Lack of etiological *evidence* due to the dearth of empirical study of P-ELBD should not equate to the lack of identifiable pathophysiological mechanisms in and of themselves.

Various studies have cited P-ELBD as psychosomatic owing to the overlap in symptoms with anxiety or panic disorders (e.g., hyperventilation). However, this concept should be considered with caution. Many disorders have similar symptoms, but that does not *necessarily* mean that these disorders come from the same etiological entity. For example, cardiac ischemia, pleural disease, and reflux disorders can all present with chest pain; however, the underlying mechanisms relating to the heart, lungs, and GI system, respectively, are all quite different. Assuming chest pain to be the same entity could result in administration of proton pump inhibitors to someone having a heart attack, which could obviously result in serious consequences. Finally, various studies reported symptoms of P-ELBD improved with behavioral interventions (e.g., cognitive behavioral therapy, psycho-educational counseling, hypnosis, positive placebos, and sedation). Unfortunately, it is unclear whether these behavioral interventions treat the underlying pathology or just the *perception* of symptoms and their severity, and the effectiveness of psychotherapy for P-ELBD is unknown due to experimental design constraints (Guglani et al., 2014).

Psychological factors as *consequential* to dyspneic-symptoms in P-ELBD have also been considered. Dyspnea may elicit the body's internal "alarm system", resulting in activation of the sympathetic "fight or flight" response (Hicks et al., 2008; Mathers-Schmidt, 2001). For example, a study by Ley (1985) demonstrated agoraphobics experience feelings of fear and panic as a *result* of episodes of physiological symptoms of hyperventilation. Additionally, Nascimento and colleagues (2013) found increased burnout, perceptions of inadequate accomplishment, reduced confidence, feelings of isolation, and issues with athletic identity in elite athletes with P-ELBD. The authors hypothesized these symptoms were what led to the P-ELBD. However, any individual who feels s/he is unable to meet personal goals or standards due to a physiological limitation (i.e.,

reduced athletic performance *due* to ELBD), or where self-identity comes into question, would undeniably exhibit the above symptoms. Furthermore, chronic stress as a consequence of fear of a dyspneic event (and resultant poor performance) has been shown to result in physical factors (e.g., expiration, muscle fatigue), perpetuating a vicious cycle, where exhaustion/fatigue from stress causes proliferation of poor performance, which then causes additional stress, propagating dyspneic events (Weinberg & Gould, 2011).

To clarify, it is not to say psychological factors do not *influence* P-ELBD, do not *co-occur* with P-ELBD, or there is no *correlation* to P-ELBD. It is just that P-ELBD as a primary psychosomatic disorder is currently an unsubstantiated claim and should not be assumed to be the underlying mechanism until a causal relationship can be appreciated. Recent literature suggests individuals with P-ELBD are not wishfully or willingly dyspneic, and symptoms of dyspnea most likely do not represent symbolic needs that are not being met, such as attention or protection (Bernstein, 2014; Martínez-Lavín & Hermosillo, 2000). Even if maladaptive brain activity is determined to be the underlying cause of P-ELBD, focus on the neurophysiological and neuromechanical functions and pathways in relation to the larynx-pulmonary system is a far more fruitful venture.

Additionally, erroneously labeling a patient "somatic" or "malingering" merely because (1) they have similar symptoms to patients with hyperventilation, (2) because their symptoms improve with cognitive-behavioral therapy, or (3) because they have anxious personalities, can have negative consequences on the efficacy of management in P-ELBD, and will most likely result in the individual seeking treatment elsewhere. This section ends with a cautionary tale to illustrate the importance of using restraint as not to assume the etiology of a pathological process without

direct causal research. Interestingly, the history of asthma[32] and its approaches to understanding its underlying mechanisms was historically addressed in the same manner as P-ELBD traditionally has been addressed. Although asthma is now known to be a *physiological* disorder involving chronic inflammation of the lower respiratory system (most likely due to a combination of genetic and environmental factors), between the 1930-1950s, asthma was considered one of the "seven holy psychosomatic illnesses," and was managed as such (Dunbar, 1948). A child's wheeze was thought to be a suppressed cry for his mother, and the standard of care was psychoanalysis and "talk therapy" (Opolski & Wilson, 2005). Unfortunately, the prevalent psychological assumption undermined years of medical and pharmacological research in this area (Brown, 2003). Luckily, in the 1970s, an appreciation for inflammatory processes involved in various diseases paved the way to studying pathophysiological mechanisms specific to asthma. Just as the concept of the asthmatic wheeze as a "suppressed cry" is viewed in today's times as archaic, laryngeal obstruction as the "body's need to protect itself," or to elicit primary or secondary gain, may be perceived in the same fashion with better appreciation of underlying pathophysiological mechanisms of P-ELBD. It is not to say psychological factors have no influence on asthma. In fact, stress and anxiety are known phenotypic *triggers* in asthma, and play a role in asthma exacerbation. However, the underlying *etiology* of asthma is patently physiological (i.e., inflammatory mechanisms), not psychosomatic and extrapolation into its pathogenesis should be treated with caution. Physiological responses to acute and prolonged stressors using cardiovascular parameters, electromyography (EMG), and brain imaging can all improve our understanding of P-ELBD. As

[32] and various other disease processes, such as rheumatologic and autoimmune diseases, as well as spasmodic dysphonia (a focal dystonia treated successfully with Botox injection) (Moran, 1996).

mentioned in Section 6.2 (Study Limitations), physiological responses to psychological stressors should be addressed in future studies.

6.4 CONCLUSION

Episodic laryngeal breathing disorders have been acknowledged for more than 140 years, yet they are still not well understood. A large part of this has to do with the larynx and its multitasking abilities. What the larynx lacks in size, it makes up for in functional versatility. It is at the helm of vital biological function, protecting the lower respiratory system and mediating respiration for life-sustaining purposes. Humans can communicate, sing, laugh, swallow, dive into a pool without drowning, give birth, and win heavy-weight championships, all with the help of the larynx. With the larynx's ability to take on so many roles, it is no wonder any number of mechanisms can result in its pathology. Even within the same laryngeal role (i.e., respiratory modulation), a broad range of endogenous and exogenous influences can affect the larynx, causing perplexing clinical presentation variants. As a result, elaborate and comprehensive frameworks, coupled with multidisciplinary collaboration and systematic interdisciplinary approaches, are needed to elucidate the multidimensional and multifactorial spectrum of ELBD.

To the dissertation candidate's knowledge, this is the first study to compare laryngeal signs and self-reported symptom differences between rest and exercise in participants with and without one ELBD variant—exercise-induced ELBD—in the same prospective study design. The study's broad inclusion of various potential characteristics attributed to ELBD afforded a Gestalt appreciation for features specific to the E-ELBD variant. The comparison group provided a normative comparison to differentiate typical responses to exercise challenge from pathological

responses. Study results highlight the clinical utility of laryngoscopy with concurrent provocation to accurately identify patients with E-ELBD. Improved quantitative methods and benchmarks to identify E-ELBD will reduce misdiagnosis and mismanagement. Studies addressing autonomic function, respiratory muscle responses, somatosensory integration, gas exchange, and laryngeal patterns are all reasonable next steps to help elucidate mechanisms underlying clinical characteristics in E-ELBD, as well as irritant-induced and psychosomatically-associated ELBD.

APPENDICES

APPENDIX A: EPISODIC LARYNGEAL BREATHING DISORDERS NOMENCLATURE

COLOR KEY
Glottic
Supraglottic
Either/Both
Unknown

1	Acquired upper airway obstruction (Hammer, 2004)
2	Adductor (laryngeal) breathing dystonia (Grillone, Annino, Blitzer, Brin, & Saint-Hilaire, 1994; Lew et al., 1994)
3	(Adult) spasmodic croup (Collett, Brancatisano, & Engel, 1983b; Kattan & Ben-Zvi, 1985; Orenstein, 2001)
4	Arytenoid variant VCD (seen on SIG3 Listserve on 11/3/15 by Andrea Storie. Email communication)
5	Asthma-like disorder (Bisgaard & Szefler, 2007, 2007; Bucca, Rolla, Brussino, De Rose, & Bugiani, 1995a, 1995b; Helenius et al., 2004; Löwhagen, 1999; Löwhagen, Arvidsson, & Pettersson, 2002; Millqvist, 2000; Millqvist, Bende, & Löwhagen, 1998; Millqvist & Löwhagen, 1996, 1996; Ringsberg & Åkerlind, 1999, 1999; Ringsberg, Lepp, & Finnström, 2002; Ringsberg, Löwhagen, & Sivik, 1993a; Ringsberg et al., 1993a; Ringsberg, Löwhagen, & Sivik, 1993b; Ringsberg, Wetterqvist, Löwhagen, & Sivik, 1997; Yüksel, Yilmaz, Kirmaz, Aydoğdu, & Kasirga, 2006)
6	Asthmatic extra thoracic upper airway obstruction (Bucca et al., 1995a).
7	Atypical asthma (King, Thompson, & Johnson, 1989)
8	Central airway obstruction (Ernst, Feller-Kopman, Becker, & Mehta, 2004; Orkin, 1974)
9	Chronic breathing disorders (Kunik et al., 2007)
10	Dysfunctional breathing (disorder) (Courtney et al., 2011; de Groot, Duiverman, & Brand, 2013; Jones, Harvey, Marston, & O'Connell, 2013; Jones, Harvey, Marston, & O'Connell, 2013; Thomas, McKinley, Freeman, & Foy, 2001)
11	Dystonic respiratory stridor (Brin & Blitzer, 1991; Payne et al., 2014)
12	Emotional laryngeal wheezing (Rodenstein, Francis, & Stănescu, 1983; Salkin, 1984)
13	Emotional laryngospasm (Liistro et al., 1990)
14	Episodic laryngeal dyskinesia (Ârez & Rivera, 1986)

15	Episodic (paroxysmal) laryngospasm (Gallivan & Andrianopoulos, 2004; Gallivan et al., 1996; Lion-Francois et al., 2010)
16	Exercise-induced inspiratory symptoms (EIIS) (Røksund et al., 2016; Campos et al., 2014)
17	Exercise-induced laryngeal dysfunction (Maat et al., 2007)
18	Exercise-induced laryngeal obstruction (Christensen et al., 2013; Christensen, Thomsen, Rasmussen, & Backer, 2011; Christensen & Rasmussen, 2013; Christensen et al., 2010; Johansson et al., 2015; Maat, 2011; Maat et al., 2009, 2011; Nielsen, Hull, & Backer, 2013)
19	Exercise-induced laryngomalacia (Bent et al., 1996; Chemery et al., 2002; Smith et al., 1995; Tilles, Ayars, Picciano, & Altman, 2013)
20	Exercise-induced laryngospasm of emotional origin (Liistro et al., 1990).
21	Exercise-induced paradoxical vocal fold motion (Mathers-Schmidt & Brilla, 2005)
22	Exercise-induced stridor (Fahey et al., 2005; Olin et al., 2014)
23	Exercise-induced vocal cord dysfunction (Davis, Brugman, & Larsen, 2007; Heinle et al., 2003; Tilles & Inglis, 2009)
24	Expiratory vocal cord dysfunction (Echternach et al., 2008; El-Kersh et al., 2014)
25	Factitious asthma (Downing et al., 1982a; Downing, Braman, Fox, & Corrao, 1982b)
26	False croup (Kjellberg, 1949)
27	Familial Munchausen stridor (McGrath, Greenberger, Zeiss, & others, 1984)
28	Functional breathing disorder (Balkissoon & Kenn, 2012; Niggemann, 2010; Ringsberg, Löwhagen, & Sivik, 1993c)
29	Functional laryngeal dyskinesia (Ferris, Eisele, & Tunkel, 1998; Renz, Hern, Tostevin, Hung, & Wyatt, 2000)
30	Functional laryngeal obstruction (Peces et al., 1995; Pitchenik, 1991)
31	Functional laryngeal stridor (Ferris et al., 1998; Renz et al., 2000)
32	Functional stridor (Kuppersmith, Rosen, & Wiatrak, 1993; Tousignant & Kleiman, 1992)
33	Functional (upper) airway obstruction (Rogers, 1980)
34	Glottic dysfunction (McFadden, 1987)
35	Hysteric croup (Dunglison, 1842)
36	Hysterical stridor (Kaufman, Mohebati, & Sotolongo, 2004; Lund, Garmel, Kaplan, & Tom, 1993; Nayar, Zanak, & Ahmed, 2003; Snyder & Weiss, 1989)
37	Inspiratory obstruction (Clark, 1970; Smith & Cooper, 1981)
38	Inspiratory vocal cord dysfunction (Miller, Jungheim, Schwemmle, Schoof, & Ptok, 2014; Morris & Christopher, 2013; Olin et al., 2015b)
39	Inter-arytenoid region prolapse (Christopher & Morris, 2010)
40	Irritant-associated vocal cord dysfunction (Perkner et al., 1998)
41	Irritable larynx syndrome (Andrianopoulos et al., 2000; Morrison & Rammage, 2010; Morrison et al., 1999)
42	Irritant vocal cord dysfunction (Tonini et al., 2009)
43	Laryngeal asthma (Shao et al., 1995)
44	Laryngeal dysfunction (Carr, Spier, Kortz, & Hoffman, 1996; Koike, 1973; O'Hollaren, 1990; Ryan & Gibson, 2009; Ryan et al., 2009; Whited, 1979; Wood, Jafek, & Cherniack, 1986)
45	Laryngeal dyskinesia (Denoyelle, Garabedian, Roger, & Tashjian, 1996)

46	Laryngeal hyperresponsiveness (Ayres & Gabbott, 2002)
47	Laryngeal hypersensitivity syndrome (Vertigan et al., 2013)
48	Laryngeal (sensitivity) dysfunction (Ryan & Gibson, 2009; Vertigan et al., 2013)
49	Laryngeal spasm (Afshan, Chohan, Qamar-Ul-Hoda, & Kamal, 2002; Chawla, Upadhyay, & MacDonnell, 1984; Cozanitis, Leijala, Pesonen, & Zaki, 1982; Fink, 1955; Murtagh & Campbell, 1954; Sasaki & Suzuki, 1977; Vas, Parsonage, & Lord, 1965)
50	Laryngeal stridor (Crooks, 1954; Morley, 1969; Yamaguchi, Arai, Asahina, & Hattori, 2002)
51	Laryngismus fugax (Pender, 1984)
52	Laryngismus stridulous (Bryan, 1891; Johnson, 1875; Klenner, 2013; Leo & Konakanchi, 1999; Perkins, 1924; Powell, 1876)
53	Laryngospasm (Alalami, Ayoub, & Baraka, 2008; Chung & Rowbottom, 1993; Maceri & Zim, 2001; Mortero, Orahovac, Tsueda, Bumpous, & others, 2001; Orenstein, 2001; Roy & Lerman, 1988)
54	Munchausen stridor (McGrath et al., 1984; Patterson et al., 1974)
55	Non-organic stridor (LaRouere & Koopnann Jr, 1987)
56	Non-organic (acute) upper airway obstruction (Ayres, Rees, & Cochrane, 1981; Neel & Posthumus, 1983; Cormier, Camus, & Desmeules, 1980)
57	Occupational vocal cord dysfunction (Muñoz et al., 2007)
58	Paradoxical arytenoid movement (PAM) (seen on SIG3 Listserve on 11/3/15 by Dale Gregore, Emai communication. No citations seen)
59	Paradoxic(al) vocal cord motion (Martin et al., 1987)
60	Paradoxical vocal cord adduction (Hayes, Nolan, Brennan, & FitzGerald, 1993; Mullinax & Kuhn, 1996)
61	Paradoxical vocal cord dysfunction (Bhargava, Panitch, & Allen, 2000; Chiang et al., 2008; Freedman et al., 1991; Heatley & Swift, 1996; Leo & Konakanchi, 1999b; Newsham, Klaben, Miller, & Saunders, 2002; Powell et al., 2000)
62	Paradoxical vocal cord movement (disorder) (Vertigan, Gibson, et al., 2007; Rogers & Stell, 1978; Omland & Brøndbo, 2008; Gallivan, 2001; Chalhoub, Harris, Sasso, & Bourjeily, 2011; Neustein, Taitt-Wynter, & Rosenblatt, 2010)
63	Paradoxical vocal fold dysfunction (Husein et al., 2008; Nacci et al., 2010; Ruddy et al., 2004; Treole et al., 1999)
64	Paradoxical vocal fold motion (Altman et al., 2002; Altman, Mirza, Ruiz, & Sataloff, 2000; Cukier-Blaj et al., 2008; Doyle et al., 2008; Forrest et al., 2012; Gurevich-Uvena et al., 2010; Guss & Mirza, 2006; Hatzelis & Murry, 2012; Hicks et al., 2008; Mathers-Schmidt, 2001b; Mathers-Schmidt & Brilla, 2005; Maturo et al., 2011; Murry et al., 2011; Murry & Sapienza, 2010; Olivier et al., 2013; Rafizadeh & Long, 2013; Sandage & Zelazny, 2004; Vasudev, 2012; Warnes & Allen, 2005)
65	Paradoxical vocal fold motion disorder (Chiang et al., 2013; Gallena & Kerins, 2013; Marcinow, Thompson, Chiang, Forrest, & Desilva, 2013; Murry, Tabaee, Owczarzak, & Aviv, 2006; Westby, 2014; Kürşat Yelken, Güven, Aladağ, & Eyibilen, 2009)
66	Paradoxical vocal fold motion dysfunction (Kursat Yelken et al., 2010)
67	Paradoxical vocal fold movement (Blager, 2000; Franca, 2014; Gallivan & Andrianopoulos, 2004; Koufman & Block, 2008; Patel, Venediktov, Schooling, & Wang, 2015; Pinho et al., 1997; Ryan et al., 2009; Shobha Sharma & Singh, 2007; van Griethuysen, Yaghchi, & Sandhu, 2012; Vertigan et al., 2006; Vertigan, Theodoros,
68	Paroxysmal laryngospasm (Loughlin & Koufman, 1996; Wani & Woodson, 1999)

69	Pediatric bilateral vocal cord dysfunction (Steiner, Fink, & Berkowitz, 2013)
70	Pseudoasthma (Chiba, Beck, Scanlon, Staats, & Mottram, 1996; Dailey, 1976; Hammo & Weinberger, 1999; Imam & Halpern, 1994; Lillington, 1981; Lillington & Lin, 1994)
71	Pseudo-steroid-resistant asthma (Ayres, 1999; Thomas, Geddes, & Barnes, 1999)
72	Psychogenic respiratory distress (Leo & Konakanchi, 1999a; Walker, Alessi, Digre, & McLean, 1989; Perera et al 2017)
73	Psychogenic stridor (Geist & Tallett, 1990; Lacy & McManis, 1994a, 1994b; Skinner & Bradley, 1989; Smith, 1983; Tomares, Flotte, Tunkel, & Loughlin, 1993)
74	Psychogenic upper airway obstruction (Barnes, Grob, Lachman, Marsh, & Loughlin, 1986; Kissoon, Kronick, & Frewen, 1988)
75	Psychogenic vocal cord dysfunction (Brown, Merritt, & Evans, 1988; Mobeireek, Alhamad, Al-Subaei, & Alzeer, 1995)
76	Psychogenic wheezing (Goldman & Muers, 1991)
77	Psychosomatic stridor and wheezing (Brashear, 1987)
78	Reactive airways dysfunction syndrome (Alberts & Guillermo, 1996; Bardana, 1999; Brooks, Weiss, & Bernstein, 1985; Gautrin, Bernstein, Brooks, & Henneberger, 2006; Kipen, Blume, & Hutt, 1994; Leroyer, Malo, Girard, Dufour, & Gautrin, 1999)
79	Reversible upper airway obstruction (Irwin, Pratter, Holland, Corwin, & Hughes, 1984)
80	Spasmodic croup (Collett et al., 1983b; Koren, Frand, Barzilay, & MacLeod, 1983; Peltola, 1983; Wolf, 1966)
81	Sporadic Apnea (Paydarfar 1995)
82	Stress-inducible functional laryngospasm (Schmidt, Brugger, & Richter, 1985)
83	Suffocative laryngismus (Rhodes, 1892)
84	Upper airway obstruction misdiagnosed as asthma (Coleman & Cooper, 1989)
85	Variable extrathoracic airflow obstruction (Das et al., 1999)
86	Variable vocal cord dysfunction (Kivity et al., 1986)
87	Vocal cord dysfunction (Ahrens, Seibt, & Kitz, 2001; Al-Alwan & Kaminsky, 2012; Amimoto et al., 2012; Anbar & Hehir, 2000; Ayres & Gabbott, 2002; Ayres & Mansur, 2011; Bahrainwala & Simon, 2001; Balkissoon & Kenn, 2012; Benninger et al., 2011; Bernstein, 2014; S. Brugman, 2003; S.M.; Brugman & Newman, 1993; Brugman & Simons, 1998; Caraon & O'toole, 1991, 1991; Cheng et al., 2013; Cho et al., 2012; Christopher, 2006; Christopher et al., 1983; Christopher & Morris, 2010; Cline et al., 2006; Cohen, 2010; Cohen & Bellucci, 2011; Cummings et al., 2013; Deckert & Deckert, 2010; de la Hoz et al., 2008; Doshi & Weinberger, 2006; Earles, Kerr, & Kellar, 2003; Echternach, Verse, Delb, & Richter, 2009; Filaire et al., 2001; Fowler, Gore, Vyas, & Haines, 2010; Frank-Ito, Schulz, Vess, & Witsell, 2015; Gimenez & Zafra, 2011; Goldman & Muers, 1991; Greenberger & Grammer, 2010; Guglani et al., 2014; Hamberg & Karlsson, 2014; Heinle et al., 2003; Herin et al., 2012; Hicks et al., 2008; Holmes et al., 2009; Hoyte, 2013; Huggins et al., 2004; Jain et al., 2006; Jamilla et al., 2000; Kenn & Balkissoon, 2011; Kenn & Hess, 2008; Kenn & Schmitz, 1997; Landwehr, Wood II, Blager, & Milgrom, 1996; MacConnell et al., 2014; McFadden & Zawadski, 1996; McQuaid, Spieth, & Spirito, 1997; Meltzer et al., 1991; Mikita & Mikita, 2006; Mikita & Parker, 2006; Morris & Christopher, 2010; Morris et al., 1999; Morris, Oleszewski, Sterner, & Allan, 2013; Morris et al., 2006; Nascimento et al., 2013; Newman et al., 1995; Newman, 2003; Newman & Dubester, 1994; Niggemann et al., 1998; Nolan, Chrysler, Phillips, Goodman, & Rusakow, 2007; Noyes & Kemp, 2007; Nugent, Nugent, Whisman, White, & Hagan, 2003; Parker & Berg, 2002; Parsons et al., 2010; Patterson &

	O'Connell, 1994; Perkins & Morris, 2002; Peters et al., 2003; Rameau, Foltz, Wagner, & Zur, 2012; Rhodes, 2008; Richards-Mauzé & Banez, 2014; Kenneth W. Rundell & Weiss, 2013; Selner et al., 1987; Sokol, 1993; Sullivan et al., 2001; Suttithawil, Chakkaphak, Jaruchinda, & Fuangtong, 2006; Tajchman & Gitterman, 1996; Taramarcaz et al., 2004; Tilles et al., 2013; Traister, Fajt, Whitman-Purves, Anderson, & Petrov, 2013; Vlahakis et al., 2002; Watson et al., 2009; Wilson & Wilson, 2006; Wood II & Milgrom, 1996; Young, Finn, Fox, Emery, & Bruetman, 2008)
88	Vocal cord dysfunction syndrome (Nastasi, Howard, Raby, Lew, & Blaiss, 1997)
89	Vocal cord malfunction (Kattan & Ben-Zvi, 1985)
90	Vocal fold motion impairment (VFMI) (Ongkasuwan et al., 2016)
91	Work-associated irritable larynx syndrome (Anderson, 2015; Hoy, Ribeiro, Anderson, & Tarlo, 2010)
92	Work-related laryngeal syndromes (Hoy, 2012)

APPENDIX B: EARLY ADOLESCENT TEMPERAMENT QUESTIONNAIRE – FEAR SUBSCALE

On this questionnaire, you will find statements that people might use to describe themselves. The statements refer to a wide number of activities and attitudes. For each statement, please circle the answer that best describes how true each statement is for you. There are no best answers. People are very different in how they feel about these statements.

1 - Almost always untrue

2 - Usually untrue

3 - Sometimes true, sometimes untrue

4 - Usually true

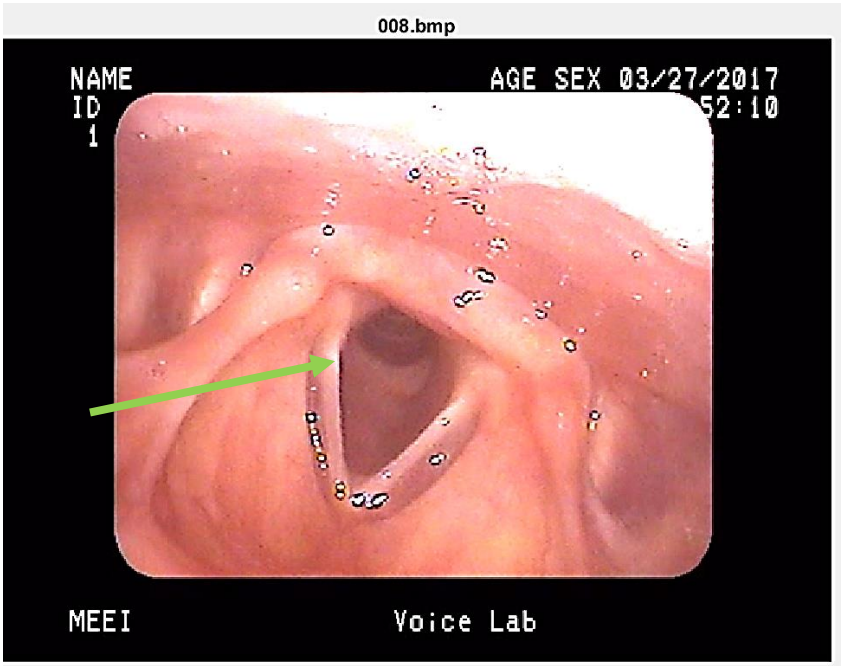
5 - Almost always true

I feel scared when I enter a dark room at home	1 2 3 4 5
I worry about my family when I'm not with them	1 2 3 4 5
I get frightened riding with a person who likes to speed	1 2 3 4 5
I worry about my parent(s) dying on me	1 2 3 4 5
I worry about getting into trouble	1 2 3 4 5
I am nervous about some of the kids at school who sometimes push people into lockers and through other kids' books around	1 2 3 4 5

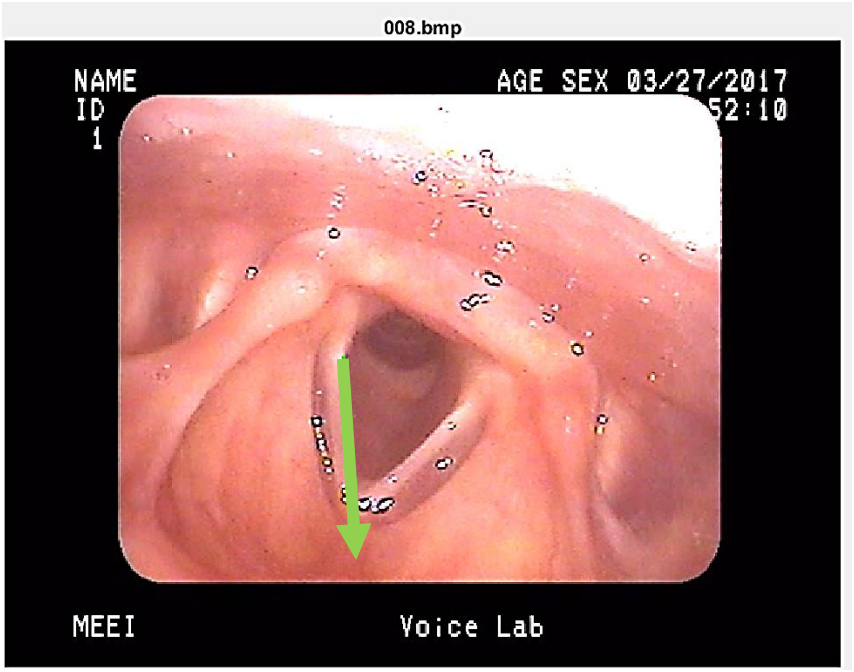
APPENDIX C: ANTERIOR GLOTTAL CONFIGURATION INSTRUCTIONS FOR RATERS

(1) Identify the following coordinates by clicking your mouse, using the following laryngeal landmarks:

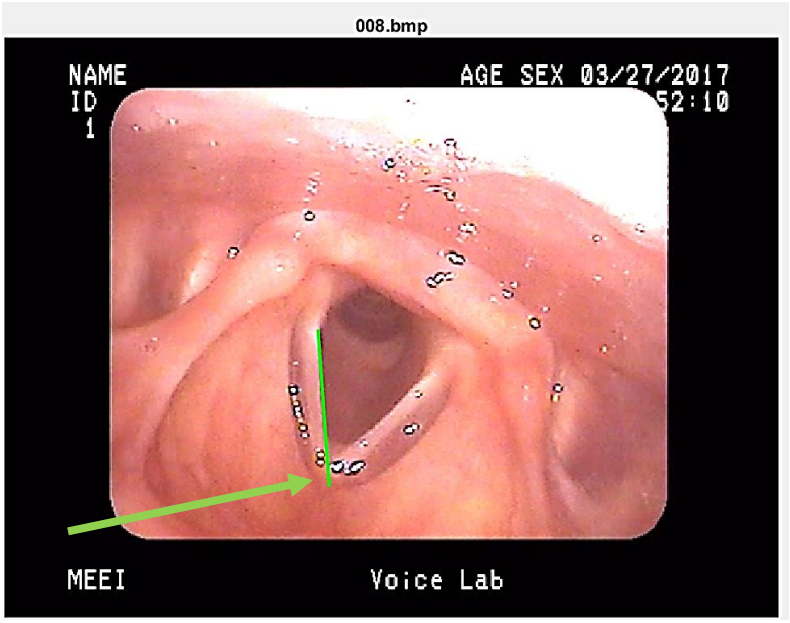
(2) **Single click** on medial tip of the **right** vocal process



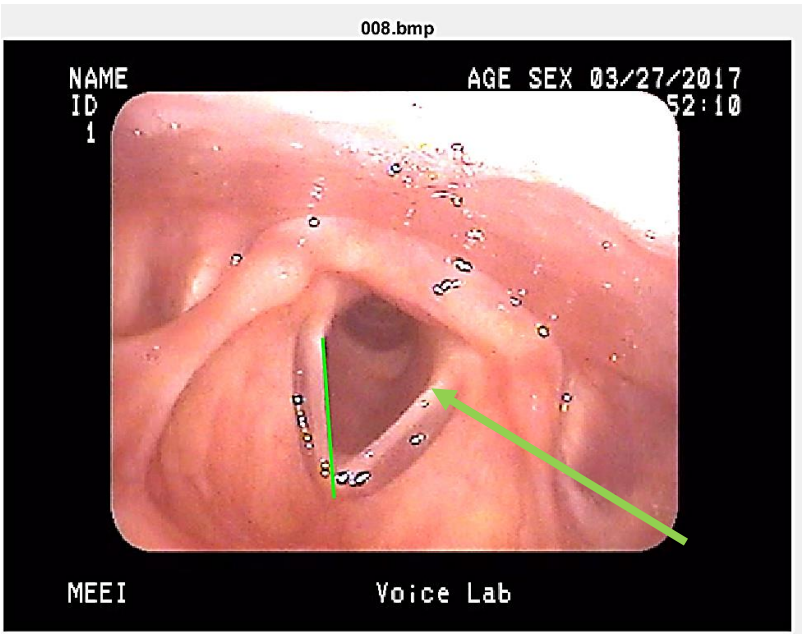
Follow <u>medial edge of superior surface of</u> **right** vocal fold to the <u>vertex of the anterior commissure</u> (or slightly passed)



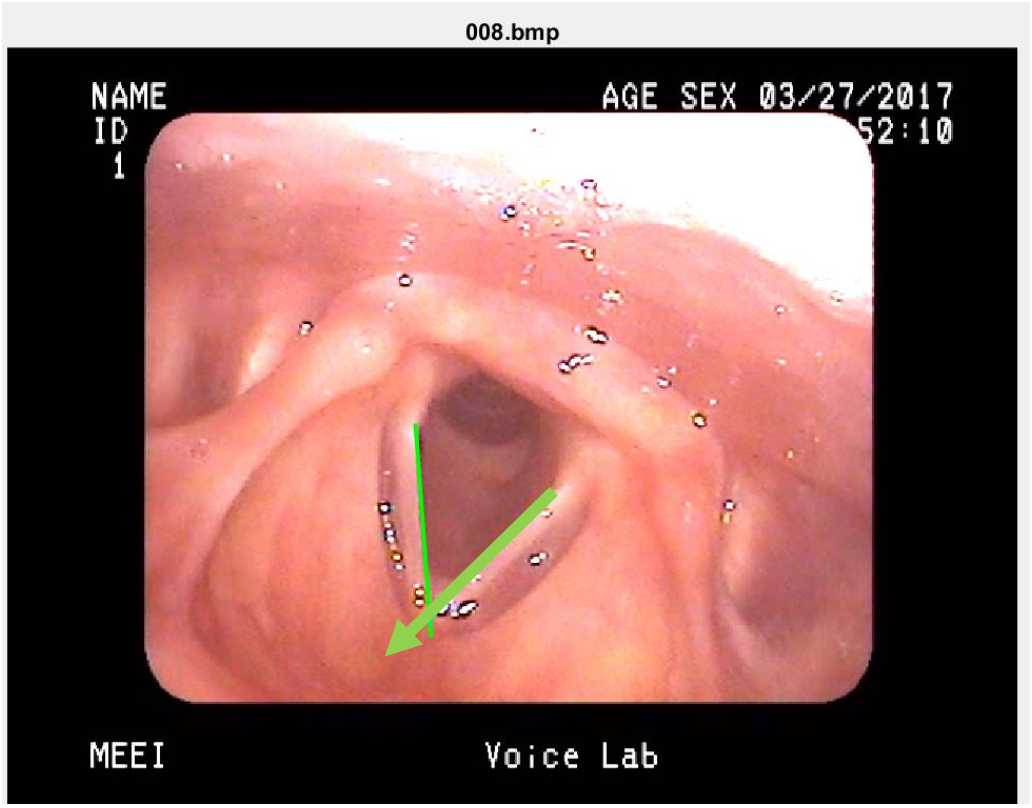
(B) **Double click** at vertex of anterior commissure (or slightly anterior).

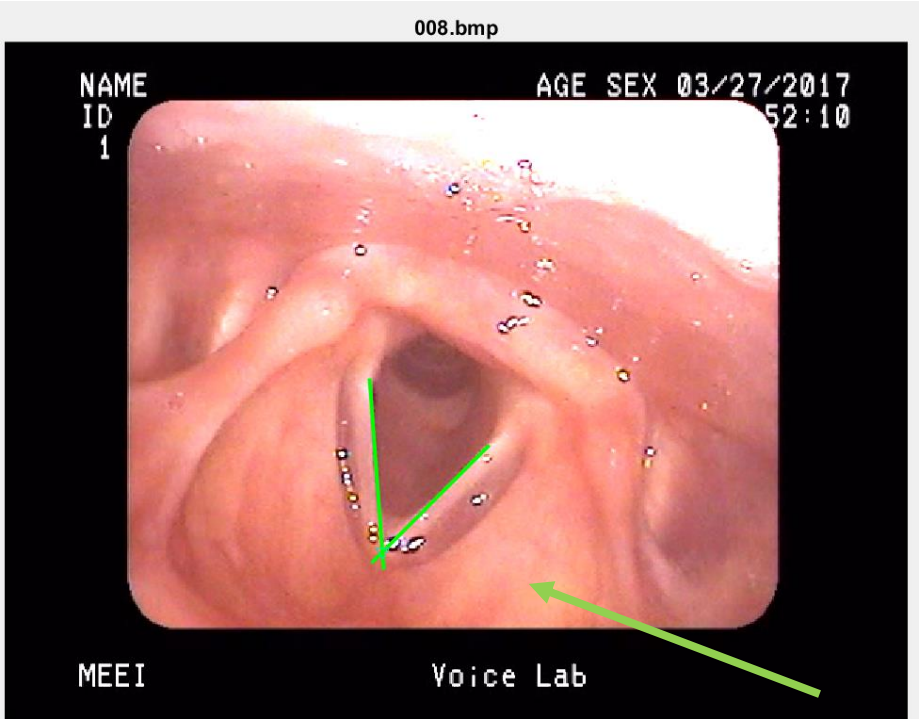


(C) **Single click** on medial tip of the **left** vocal process



Follow medial edge of superior surface of **left** vocal fold to the vertex of the anterior commissure (or slightly beyond).



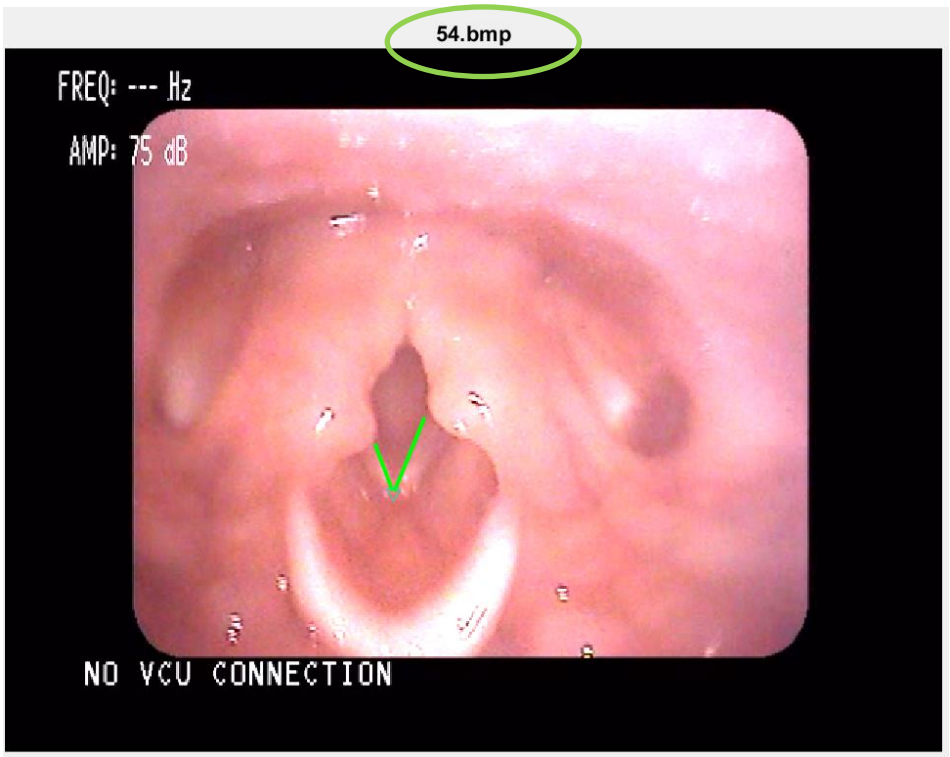


(D) **Double click** at vertex of anterior commissure.

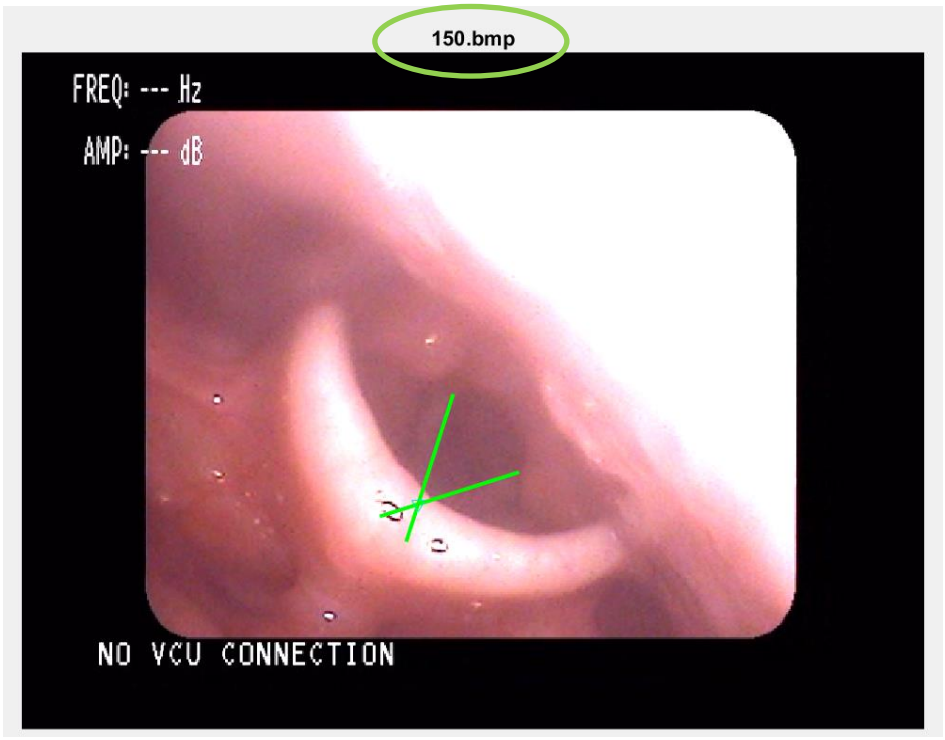
To accept, hit **ENTER**

To redo, hit any other key, and then ENTER

(3) If the vocal process is obstructed (e.g., arytenoid prolapse), drop coordinates anterior to the vocal process and follow the marginal edges of the superior vocal fold (posterior to anterior) to vertex (or slightly anterior) of anterior commissure. Then indicate as "posterior obstruction" with image number (found at the top of the image [#.bmp]) to Adrianna.



(4) If the anterior commissure is occluded (e.g., epiglottic collapse), follow the marginal edges of the superior true vocal folds (posterior to anterior) until crosshairs are created



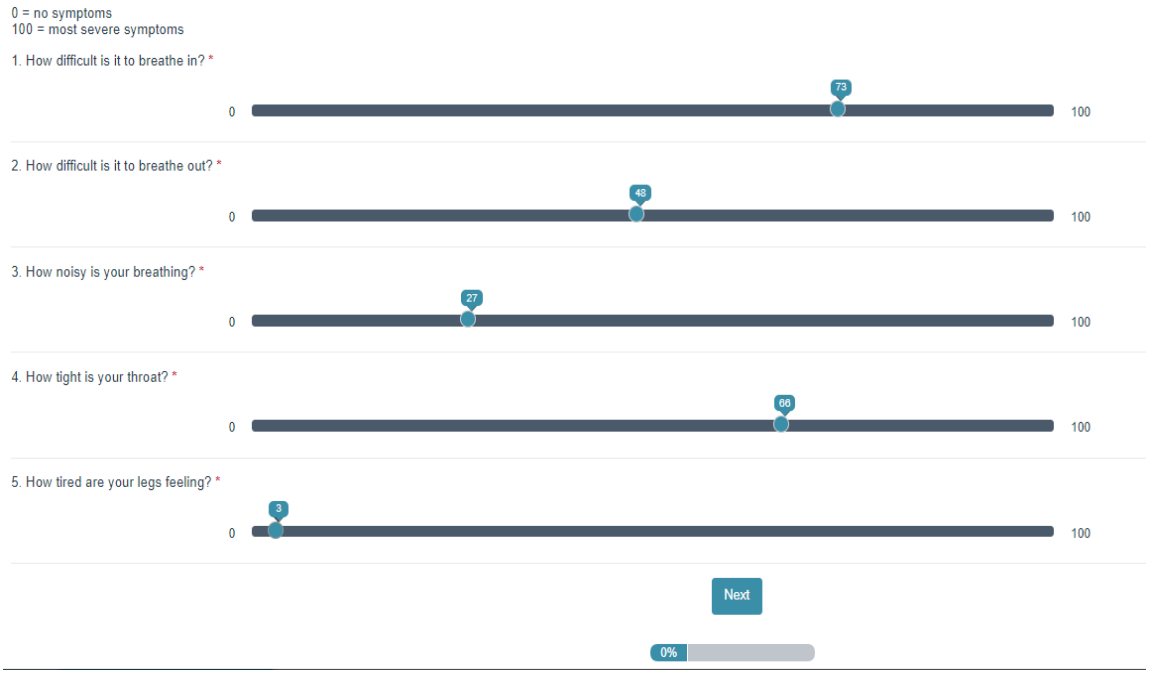
near the anterior commissure (see example below). Then indicate as “anterior occlusion” with image number (found at the top of the image [#.bmp]) to Adrianna.

(5) If the entire glottal region is occluded, indicate “total occlusion” with image number (found at the top of the image [#.bmp]) to Adrianna.

(6) If the image is so poor that you aren’t comfortable with your measurement, say “poor image” with the number.

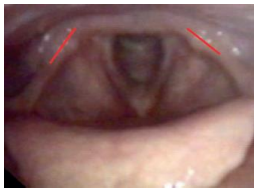
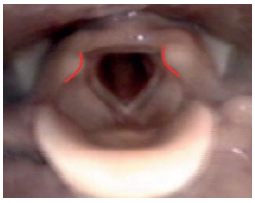
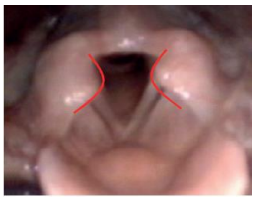
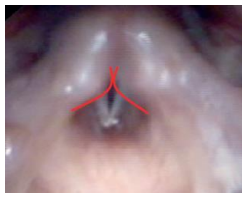
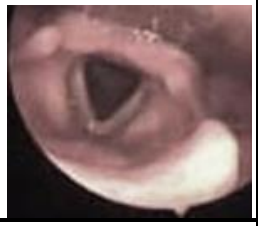
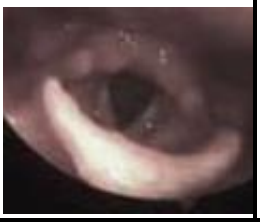
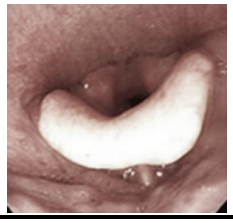
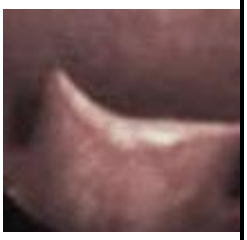
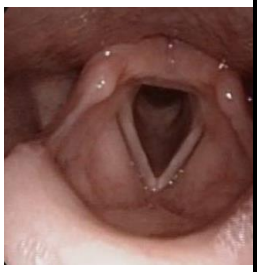
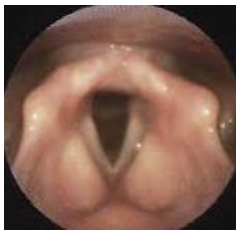
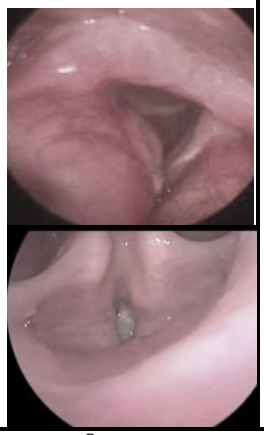
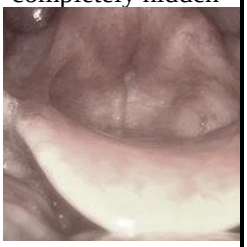
(7) Ignore humps, bumps, and lumps on vocal folds, when following the line from the posterior process to anterior commissure

APPENDIX D: VISUAL ANALOG SCALE PERCEPTUAL RATINGS



APPENDIX E: SUPRAGLOTTIC MOVEMENT INSTRUCTIONS FOR RATERS

Indicate the number corresponding to the severity of laryngeal obstruction for each loci of obstruction on excel spreadsheet (see below for reference):

Obstruction Type	0	1	2	3
Arytenoid prolapse[1]	Expected maximal abduction of the aryepiglottic folds with no visible medial rotation (top of cuneiform tubercles pointed vertical or slightly lateral) 	Visual medial rotation of the cranial edge of the aryepiglottic folds and tops of the cuneiform tubercles 	Further medial rotation of the cuneiform tubercles with exposure of the mucosa on the lateral sides of the tubercles 	Medial rotation until near horizontal position of the cuneiform tubercles and tops of the cuneiform tubercles move towards the midline 
Epiglottic Collapse[2]	Epiglottis hugs the tongue 	Epiglottis between 0-45° 	Epiglottis between 45-90° 	Epiglottis over 90° 
Ventricular (False) Fold compression[3]	Absent 	1/3 of the true vocal folds covered 	2/3 of the true vocal folds covered 	True vocal folds completely hidden 

[1]Validated by Maat (2011); [2]validated by Catalfumo et al., (1998); [3]validated by Schonweile et al (1998)

APPENDIX F: DYSPNEA INDEX

Dyspnea Index – Revised

Subject ID: _____

Date: ___/___/_____

Below are some symptoms that you may be feeling.
Please circle the number that indicates how often you feel these symptoms.

(0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, 4 = always)

1.	I have trouble getting air in.	0 1 2 3 4
2.	I feel tightness in my throat when I am having my breathing problem.	0 1 2 3 4
3.	It takes more effort to breathe than it used to.	0 1 2 3 4
4.	Changes in weather affect my breathing problem.	0 1 2 3 4
5.	My breathing gets worse with stress.	0 1 2 3 4
6.	I make sound/noise breathing in.	0 1 2 3 4
7.	I have to strain to breathe.	0 1 2 3 4
8.	My shortness of breath gets worse with exercise or physical activity	0 1 2 3 4
9.	My breathing problem makes me feel stressed	0 1 2 3 4
10.	My breathing problem causes me to restrict my personal and social life.	0 1 2 3 4

APPENDIX G: RESPIRATORY RETRAINING THERAPY (CONCEPTUAL)

Respiratory retraining therapy (RRT) – also known as *laryngeal control therapy*, *breathing retraining*, and *speech therapy*, among others – is the standard of care for individuals with ELBD (Doshi & Weinberger, 2006; Hatzelis & Murry, 2012; Hoyte, 2013; Matrka, 2014; Murry et al., 2011; Nacci et al., 2010; Sandage & Zelazny, 2004). RRT is comprised of various breathing exercises using focused abdominal breathing and a semi-occluded vocal tract to slow down rate of breathing and regulate breathing patterns; RRT may also be used to reduce arousal and stress levels that can result from the these abnormal breathing rates and patterns (Chapell, 1994; Greenberger & Grammer, 2010; Husein et al., 2008; Newman, 2003; Powell et al., 2000). Although RRT is considered the "gold standard" for management of ELBD, the efficacy of RRT, to date, has not been empirically tested and is largely based on anecdotes and expert opinion.

Principles central to RRT include: (1) understanding of the anatomy and physiology of the larynx and systems involved in ELBD, (2) increased self-awareness of one's own breathing patterns, (3) increased self-awareness of physical stress and tension, (4) the use of restorative breathing patterns, (5) incorporation of new breathing patterns during movement and activity, and (6) application of breathing techniques during acute episodes (CliftonSmith & Rowley, 2011). To address these principles, RRT involves three components: (1) education, (2) training in supposedly optimal[33] abdominal breathing and laryngeal configuration, and (3) recovery breathing. A summary of each of these components, as well as psychological and physiological hypotheses about the underlying therapeutic mechanisms are provided next.

[33] Although was constitutes "optimal" is unclear due to the lack of empirical study of RRT and appreciation of normal respiratory laryngeal physiology, in general.

Education

The educational component to RRT involves (a) psycho-educational counseling, (b) vocal hygiene education, and (c) trigger awareness. *Psycho-educational counseling* focuses on increasing the patient's motivation to address the issues and adherence to the program,validates the patients' concerns, and empowers the patient. Activities include counseling, anatomy and physiology education, and endoscopic visual biofeedback. The SLP also provides the patient with the rationale for behavioral management (Gibson & Vertigan, 2009). *Vocal hygiene* programs help reduce laryngeal irritation that can perpetuate laryngeal hypersensitivity and dysfunction. This goal is accomplished by reducing environmental or internal irritants (e.g., noxious fumes; laryngopharyngeal reflux) and incorporating hydration (systemic and surface) to reduce irritation caused by mucosal dryness (Andrianopoulos et al., 2000). *Trigger awareness* helps the patient recognize specific environments or behaviors that need to be managed (Andrianopoulos et al., 2000; Sandage & Zelazny, 2004).

"Optimal" abdominal breathing and laryngeal configuration in respiration

Training in optimal abdominal breathing and laryngeal configuration focuses on coordination of a relaxed throat and breathing involving lower abdominal excursions during respiratory cycles. These techniques aid with the establishment of "low breath," reduce extrinsic laryngeal tension, prevent clavicular breathing, increase self-awareness, prepare the patient for voluntary breath control, and direct attention away from the larynx (Gallivan, Hoffman, & Gallivan, 1996). Steps include placing one hand on the chest and the other hand on the mid-abdomen (below the rib cage), lowering the shoulders, breathing gently in through the nose and out through pursed lips, while

allowing the abdomen to move freely. Negative practice is also incorporated. This last therapeutic strategy involves tightening and relaxing various muscles (e.g., feet, thighs, hands, lips) in order to increase bodily awareness and help the patient identify localized tension, so that he/she may actively release said tension once identified (Mathers-Schmidt, 2001; Sandage & Zelazny, 2004).

Recovery breathing

Recovery breathing involves quick inspiration (~1 second) and slower expiration on pursed lips (~2-3 seconds), while simultaneously incorporating lower abdominal breathing. A quick inspiration forces abduction of the vocal folds while expiratory pursed lip breathing slows down breathing rate and reduces state of arousal (e.g., anxiety, panic), abducts the vocal folds via increased intraoral pressure, keeps focus away from the larynx, and helps to break the dyspneic cycle (Andrianopoulos et al., 2000; Gallivan et al., 1996; Mathers-Schmidt, 2001). To reach automaticity with the task, the patient repeats recovery-breathing techniques while asymptomatic for 5 minutes intervals, 10-20 times throughout the day. The SLP then works closely with the patient to apply the techniques to the patient's individual triggers within different settings. The triggers are presented in a deliberate, yet gradual manner to increase desensitization to the triggers (Mathers-Schmidt, 2001).

Potential mechanisms underlying RRT

Various psychosocial and biomechanical hypotheses have been attributed to the putative success of RRT, but the exact mechanisms are unknown. Psychosocial hypotheses suggest RRT may increase relaxation, reduce anxiety, or give the individual an opportunity to be distracted from the

uncomfortable sensation of dyspnea by refocusing with a structured task. RRT may also promote self-reassurance, self-control, self-efficacy, self-awareness, sense of mastery, and empowerment (Garssen, de Ruiter, & Van Dyck, 1992; Han, Stegen, De Valck, Clement, & Van de Woestijne, 1996; Lum, 1983). Biomechanical hypotheses suggest lowering the larynx, depressing the base of tongue, reducing tongue tension, or abducting the vocal folds through subglottal pressure changes "optimize" oropharyngeal or laryngeal posture (Gibson & Vertigan, 2009). Future studies are needed to elucidate the facilitative mechanisms that help relieve dyspneic symptoms in patients with ELBD.

Respiratory Retraining Therapy

Laryngeal Control Postures: <u>Preventative</u>

"Open the Gate"

Think ***wide*** in throat

- Yawn
- Internal yawn/stifle smile or laugh
- Pop your ears (start to yawn but don't go into a full yawn)
- Deliberate swallow
- Thrust out tongue with exhale ("Lion's breath")
- Thrust out jaw
- Flare neck out (like saying "oops" with your neck)
- "Gimme a break" face
- Sneeze face
- Push entire tongue to roof of mouth
- Curl tongue back in mouth
- Push tongue tip to back of bottom teeth
- Cleaning back teeth (upper and lower) with tongue
- Puff cheeks up with air, briefly hold your breath, then release
- Puff cheeks up with air while breathing through nose
- Raspberries/tongue trills

Ratios: _____ : _____

Rescue Breathing: <u>Recovery</u>

- Breathe/exhale/blow out gently through puckered lips (like you are blowing candles out on a cake)
- Take a wide breath (not deep! “open the gate!”)
    - through your nose (like you’re smelling something nice)
    - through puckered lips (like you’re sucking a thick milkshake through a straw)
- Repeat cycle.

Counts:

Inhale: _____

Exhale: _____

Remember!

1. You can’t die from it
2. It’s not a breathing problem
3. We are retraining/reprogramming muscle patterns

REFERENCES

Abu-Hasan, M., Tannous, B., & Weinberger, M. (2005). Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Annals of Allergy, Asthma & Immunology*, *94*(3), 366–371.

Ahrens, P., Seibt, Y., & Kitz, R. (2001). [Vocal cord dysfunction in children and adolescents]. *Pneumologie (Stuttgart, Germany)*, *55*(8), 378–384.

Al Haddad, H., Laursen, P. B., Chollet, D., Ahmaidi, S., & Buchheit, M. (2011). Reliability of resting and postexercise heart rate measures. *International Journal of Sports Medicine*, *32*(8), 598.

Alalami, A. A., Ayoub, C. M., & Baraka, A. S. (2008). Laryngospasm: review of different prevention and treatment modalities. *Paediatric Anaesthesia*, *18*(4), 281–288.

Al-Alwan, A., & Kaminsky, D. (2012). Vocal cord dysfunction in athletes: clinical presentation and review of the literature. *The Physician and Sportsmedicine*, *40*(2), 22–27. https://doi.org/10.3810/psm.2012.05.1961

Aldrich, T. K. (1988). Respiratory muscle fatigue. *Clinics in Chest Medicine*, *9*(2), 225–236.

Altman, K. W., Simpson, C. B., Amin, M. R., Abaza, M., Balkissoon, R., & Casiano, R. R. (2002). Cough and paradoxical vocal fold motion. *Otolaryngology–Head and Neck Surgery*, *127*(6), 501–511.

Anbar, R. D. (2012). *Functional respiratory disorders: when respiratory symptoms do not respond to pulmonary treatment*. Springer.

Andrianopoulos, M. V., Gallivan, G. J., & Gallivan, K. H. (2000). PVCM, PVCD, EPL, and irritable larynx syndrome: What are we talking about and how do we treat it?*. *Journal of Voice*, *14*(4), 607–618.

Annesi-Maesano, I. (2003). Epidemiological Evidence for the Relationship Between Upper and Lower Airway Diseases. *Lung Biology in Health and Disease*, *181*, 105–128.

Appelblatt, N. H., & Baker, S. R. (1981). Functional upper airway obstruction: a new syndrome. *Archives of Otolaryngology*, *107*(5), 305–306.

Arteaga-Solis, E., Zee, T., Emala, C. W., Vinson, C., Wess, J., & Karsenty, G. (2013). Inhibition of leptin regulation of parasympathetic signaling as a cause of extreme body weight-associated asthma. *Cell Metabolism*, *17*(1), 35–48.

Ates, F., & Vaezi, M. (2014). Insight into the relationship between gastroesophageal reflux disease and asthma. *Gastroenterology and Hepatology*, *10*(11).

Atiken, R. (1969). Measurements of feelings using visual analogue scale. *Proc R Soc Med*, *62*, 989–993.

ATS, D. (1999). Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. *Am J Respir Crit Care Med*, *159*, 321–340.

Ayres, J. G., & Gabbott, P. L. A. (2002). Vocal cord dysfunction and laryngeal hyperresponsiveness: a function of altered autonomic balance? *Thorax*, *57*(4), 284–285.

Ayres, Jon G., & Mansur, A. H. (2011). Vocal cord dysfunction and severe asthma: considering the total airway. *American Journal of Respiratory and Critical Care Medicine*, *184*(1), 2–3.

Backer, V. (2010). Not all who wheeze have asthma. *Breathe*, *7*, 17–22.

Bahrainwala, A. H., & Simon, M. R. (2001). Wheezing and vocal cord dysfunction mimicking asthma. *Current Opinion in Pulmonary Medicine*, *7*(1), 8.

Baker, J., Côté, J., & Hawes, R. (2000). The relationship between coaching behaviours and sport anxiety in athletes. *Journal of Science and Medicine in Sport*, *3*(2), 110–119. https://doi.org/10.1016/S1440-2440(00)80073-0.

Balkissoon, R. (2002). Occupational upper airway disease. *Clinics in Chest Medicine*, *23*(4), 717–725.

Balkissoon, R., & Kenn, K. (2012). Asthma: vocal cord dysfunction (VCD) and other dysfunctional breathing disorders. In *Seminars in respiratory and critical care medicine* (Vol. 33, pp. 595–605).

Banzett, R. B., O'Donnell, C. R., Guilfoyle, T. E., Parshall, M. B., Schwartzstein, R. M., Meek, P. M., … Lansing, R. W. (2015). Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. *The European Respiratory Journal*, *45*(6), 1681–1691. https://doi.org/10.1183/09031936.00038914.

Barnes, P. J. (1990). Neural control of airway function: new perspectives. *Molecular Aspects of Medicine*, *11*(5), 351–423.

Barnes, P. J. (1996). Neuroeffector mechanisms: the interface between inflammation and neuronal responses. *Journal of Allergy and Clinical Immunology*, *98*(5), S73–S83.

Barnes, P. J. (2001). Neurogenic inflammation in the airways. *Respiration Physiology*, *125*(1), 145–154.

Baroody, F. M., & Canning, B. J. (2003). Comparative anatomy of the nasal and tracheal/bronchial airways. *Lung Biology in Health and Disease*, *181*, 1–43.

Barrière, J. R., Delpierre, S., Del Volgo, M. J., & Jammes, Y. (1993). Comparisons among external resistive loading, drug-induced bronchospasm, and dense gas breathing in cats: roles of vagal and spinal afferents. *Lung*, *171*(3), 125–136.

Bartulovic, D., Young, B. W., & Baker, J. (2017). Self-regulated learning predicts skill group differences in developing athletes. *Psychology of Sport and Exercise*, *31*(Supplement C), 61–69. https://doi.org/10.1016/j.psychsport.2017.04.006

Beaty, M. M., Wilson, J. S., & Smith, R. J. . (1999). Laryngeal motion during exercise. *The Laryngoscope*, *109*(1), 136–139.

Becker, M. de M. C., Silva, O. B. e, Moreira, I. E. G., & Victor, E. G. (2007). Arterial blood pressure in adolescents during exercise stress testing. *Arquivos Brasileiros de Cardiologia*, *88*(3), 329–333. https://doi.org/10.1590/S0066-782X2007000300012

Benninger, C., Parsons, J. P., & Mastronarde, J. G. (2011). Vocal cord dysfunction and asthma. *Current Opinion in Pulmonary Medicine*, *17*(1), 45.

Bent 3rd, J. P., Miller, D. A., Kim, J. W., Bauman, N. M., Wilson, J. S., & Smith, R. J. (1996). Pediatric exercise-induced laryngomalacia. *The Annals of Otology, Rhinology, and Laryngology*, *105*(3), 169–175.

Bernstein, S. M. (2014). *Improving differential diagnosis of vocal cord dysfunction*. Retrieved from http://repositories.lib.utexas.edu/handle/2152/25870

Blager, F. B. (2000). Paradoxical vocal fold movement: diagnosis and management. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *8*(3), 180–183.

Bolser, D. C., & Davenport, P. W. (2002). Functional organization of the central cough generation mechanism. *Pulmonary Pharmacology & Therapeutics*, *15*(3), 221–225.

Bolser, D. C., Poliacek, I., Jakus, J., Fuller, D. D., & Davenport, P. W. (2006). Neurogenesis of cough, other airway defensive behaviors and breathing: A holarchical system? *Respiratory Physiology & Neurobiology*, *152*(3), 255–265.

Boushey, H. A., Richardson, P. S., & Widdicombe, J. G. (1972). Reflex effects of laryngeal irritation on the pattern of breathing and total lung resistance. *The Journal of Physiology*, *224*(2), 501–513.

Brame, A. L., & Singer, M. (2010). Stressing the obvious? An allostatic look at critical illness. *Critical Care Medicine*, *38*(10), S600–S607.

Brancatisano, T., Collett, P. W., & Engel, L. A. (1983). Respiratory movements of the vocal cords. *Journal of Applied Physiology*, *54*(5), 1269–1276.

Brancatisano, T., Dodd, D., & Engel, L. A. (1983). Factors influencing glottic dimensions during forced expiration. *Journal of Applied Physiology*, *55*(6), 1825–1829.

Brancatisano, T. P., Dodd, D. S., & Engel, L. A. (1984). Respiratory activity of posterior cricoarytenoid muscle and vocal cords in humans. *J Appl Physiol*, *57*(1), 145.

Brooks, S. (2011). Anatomy of the cough reflex. *Cough*, *7*(10), 1–26.

Brouillette, R. T., & Thach, B. T. (1979). A neuromuscular mechanism maintaining extrathoracic airway patency. *Journal of Applied Physiology*, *46*(4), 772–779.

Brouillette, R. T., & Thach, B. T. (1980). Control of genioglossus muscle inspiratory activity. *Journal of Applied Physiology*, *49*(5), 801–808.

Brown, E. S. (2003). *Asthma: Social and Psychological Factors and Psychosomatic Syndromes*. Karger Medical and Scientific Publishers.

Brown, T., M., Merritt, W. D., & Evans, D. L. (1988). Psychogenic vocal cord dysfunction masquerading as asthma. *The Journal of Nervous and Mental Disease*, *176*(5), 308–310.

Brugman, S. M. (2003). The many faces of vocal cord dysfunction: what 36 years of literature tell us. *Am J Respir Crit Care Med*, *167*(7), A588.

Buchheit, M., Millet, G., Parisy, A., Pourchez, S., Laursen, P., & Ahmaidi, S. (2008). Supramaximal training and postexercise parasympathetic reactivation in adolescents. *Medicine+ Science in Sports+ Exercise*, *40*(2), 362.

Butani, L., & O'Connell, E. J. (1997). Functional respiratory disorders. *Annals of Allergy, Asthma & Immunology*, *79*(2), 91–101.

Canning, B. J., & Undem, B. J. (1994). Parasympathetic innervation of airways smooth muscle. In *Airways Smooth Muscle* (pp. 43–78). Springer. Retrieved from http://link.springer.com/chapter/10.1007/978-3-0348-7558-5_3

Capaldi, D. M., & Rothbart, M. K. (1992). Development and validation of an early adolescent temperament measure. *The Journal of Early Adolescence*, *12*(2), 153–173.

Caraon, P., & O'toole, C. (1991). Vocal cord dysfunction presenting as asthma. *Irish Medical Journal*, *84*(3), 98.

Carter, A. S., Briggs-Gowan, M. J., & Davis, N. O. (2004). Assessment of young children's social-emotional development and psychopathology: recent advances and recommendations for practice. *Journal of Child Psychology and Psychiatry*, *45*(1), 109–134. https://doi.org/10.1046/j.0021-9630.2003.00316.x.

Chaitow, L., Bradley, D., & Gilbert, C. (2013). What are breathing pattern disorders? *Recognizing and Treating Breathing Disorders*, 1.

Chandra, R. K., Gerber, M. E., & Holinger, L. D. (2001). Histological insight into the pathogenesis of severe laryngomalacia. *International Journal of Pediatric Otorhinolaryngology*, *61*(1), 31–38.

Chapell, M. S. (1994). Inner speech and respiration: toward a possible mechanism of stress reduction. *Perceptual and Motor Skills*, *79*(2), 803–811.

Chiang, W. C., Goh, A., Ho, L., Tang, J. P., & Chay, O. M. (2008). Paradoxical vocal cord dysfunction: when a wheeze is not asthma. *Singapore Medical Journal*, *49*(4), e110–2.

Christensen, P. M., Thomsen, S. F., Rasmussen, N., & Backer, V. (2011). Exercise-induced laryngeal obstructions: prevalence and symptoms in the general public. *European Archives of Oto-Rhino-Laryngology*, *268*(9), 1313–1319.

Christensen, P., Thomsen, S. F., Rasmussen, N., & Backer, V. (2010). Exercise-induced laryngeal obstructions objectively assessed using EILOMEA. *European Archives of Oto-Rhino-Laryngology*, *267*(3), 401–407.

Christopher, K. L., & Morris, M. . (2010). Vocal cord dysfunction, paradoxic vocal fold motion, or laryngomalacia? Our understanding requires an interdisciplinary approach. *Otolaryngologic Clinics of North America*, *43*(1), 43.

Christopher, K. L., Wood, R. P., Eckert, R. C., Blager, F. B., Raney, R. A., & Souhrada, J. F. (1983). Vocal-cord dysfunction presenting as asthma. *New England Journal of Medicine*, *308*(26), 1566–1570.

Chung, K. F. (2011). Chronic "cough hypersensitivity syndrome": a more precise label for chronic cough. *Pulmonary Pharmacology & Therapeutics*, *24*(3), 267–271.

CliftonSmith, T., & Rowley, J. (2011). Breathing pattern disorders and physiotherapy: inspiration for our profession. *Physical Therapy Reviews*, *16*(1), 75–86.

Cobeta, I., Pacheco, A., & Mora, E. (2013). The role of the larynx in chronic cough. *Acta Otorrinolaringológica Española*, *64*(5), 363–368. https://doi.org/10.1016/j.otorri.2012.10.001.

Collett, P. W., Brancatisano, A. P., & Engel, L. A. (1986). Upper airway dimensions and movements in bronchial asthma. *The American Review of Respiratory Disease*, *133*(6), 1143–1149.

Collett, P. W., Brancatisano, T., & Engel, L. A. (1983). Changes in the glottic aperture during bronchial asthma. *The American Review of Respiratory Disease*, *128*(4), 719.

Congenital Laryngeal Stridor (Laryngomalacia): Etiologic Factors and Associated DisordersAnnals of Otology, Rhinology & Laryngology - Judson R. Belmont, Kenneth Grundfast, 1984. (n.d.). *Annals of Otology, Rhinology & Laryngology*. Retrieved from http://journals.sagepub.com.pitt.idm.oclc.org/doi/abs/10.1177/000348948409300502.

Coote, J. H. (2010). Recovery of heart rate following intense dynamic exercise. *Experimental Physiology*, *95*(3), 431–440.

Corey, J. P., Gungor, A., & Karnell, M. (1998). Allergy for the laryngologist. *Otolaryngologic Clinics of North America*, *31*(1), 189–205.

Courtney, R., Greenwood, K. M., & Cohen, M. (2011). Relationships between measures of dysfunctional breathing in a population with concerns about their breathing. *Journal of Bodywork and Movement Therapies*, *15*(1), 24–34.

Couto, M., de Diego, A., Perpiñi, M., Delgado, L., & Moreira, A. (2013). Cough reflex testing with inhaled capsaicin and TRPV1 activation in asthma and comorbid conditions. *Journal of Investigational Allergology & Clinical Immunology*, *23*(5), 289–301.

Crisafulli, E., & Clini, E. M. (2010). Measures of dyspnea in pulmonary rehabilitation. *Multidisciplinary Respiratory Medicine*, *5*(3), 202.

Critchley, H. D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology*, *493*(1), 154–166.

Cukier-Blaj, S., Bewley, A., Aviv, J. E., & Murry, T. (2008). Paradoxical vocal fold motion: a sensory-motor laryngeal disorder. *The Laryngoscope*, *118*(2), 367–370. https://doi.org/10.1097/MLG.0b013e31815988b0.

de Carlos, F., Cobo, J., Macías, E., Feito, J., Cobo, T., Calavia, M. g., … Vega, J. a. (2013). The Sensory Innervation of the Human Pharynx: Searching for Mechanoreceptors. *The Anatomical Record*, *296*(11), 1735–1746. https://doi.org/10.1002/ar.22792

De Guzman V, Ballif CL, Maurer R, Hartnick CJ, & Raol N. (2014). Validation of the dyspnea index in adolescents with exercise-induced paradoxical vocal fold motion. *JAMA Otolaryngology–Head & Neck Surgery*, *140*(9), 823–828. https://doi.org/10.1001/jamaoto.2014.1405

de la Hoz, R. E., Shohet, M. R., Bienenfeld, L. A., Afilaka, A. A., Levin, S. M., & Herbert, R. (2008). Vocal cord dysfunction in former World Trade Center (WTC) rescue and recovery workers and volunteers. *American Journal of Industrial Medicine*, *51*(3), 161–165. https://doi.org/10.1002/ajim.20541.

De Torres, J. P., Pinto-Plata, V., Ingenito, E., Bagley, P., Gray, A., Berger, R., & Celli, B. (2002). Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. *Chest Journal*, *121*(4), 1092–1098.

deGruy, F., Columbia, L., & Dickinson, P. (1987). Somatization disorder in a family practice. *The Journal of Family Practice*, *25*(1), 45–51.

Dekhuijzen, P. N., Gayan-Ramirez, G., Bisschop, A., de Bock, V., Dom, R., & Decramer, M. (1996). Recovery of corticosteroid-induced changes in contractile properties and morphology of rat diaphragm. *American Journal of Respiratory and Critical Care Medicine*, *153*(2), 769–775. https://doi.org/10.1164/ajrccm.153.2.8564131

Dempsey, J. A., & Pack, A. I. (1995). *Regulation of breathing*. M. Dekker.

Dicpinigaitis, P. V., Lim, L., & Farmakidis, C. (2014). Cough syncope. *Respiratory Medicine*, *108*(2), 244–251. https://doi.org/10.1016/j.rmed.2013.10.020.

Dishman, R. K., Nakamura, Y., Garcia, M. E., Thompson, R. W., Dunn, A. L., & Blair, S. N. (2000). Heart rate variability, trait anxiety, and perceived stress among physically fit men and women. *International Journal of Psychophysiology*, *37*(2), 121–133. https://doi.org/10.1016/S0167-8760(00)00085-4.

Doshi, D. R., & Weinberger, M. M. (2006). Long-term outcome of vocal cord dysfunction. *Annals of Allergy, Asthma & Immunology*, *96*(6), 794–799.

Downing, E. T., Braman, S. S., Fox, M. J., & Corrao, W. M. (1982). Factitious asthma. *JAMA: The Journal of the American Medical Association*, *248*(21), 2878–2881.

Dunbar, F. (1948). Mind and body: Psychosomatic medicine. *AJN The American Journal of Nursing*, *48*(10), 40.

Dunglison, R. D. (1842). The practice of medicine. *Philadelphia: Lea and Blanchard*, *258*.

Dunn, N. M., Katial, R. K., & Hoyte, F. C. (2015). Vocal cord dysfunction: a review. *Asthma Research and Practice*, *1*(1), 9.

Earles, J., Kerr, B., & Kellar, M. (2003). Psychophysiologic treatment of vocal cord dysfunction. *Annals of Allergy, Asthma & Immunology*, *90*(6), 669–671.

Eccles, R. (2003). Upper airway reflexes and involvement of the lower airway. *Lung Biology in Health and Disease*, *181*, 87–99.

Echternach, M., Verse, T., Delb, W., & Richter, B. (2009). Exspiratorische Vocal Cord Dysfunction? *HNO*, *57*(1), 68–72.

Echternach, Matthias, Delb, W., Verse, T., & Richter, B. (2008). Does isolated expiratory vocal cord dysfunction exist? *Otolaryngology–Head and Neck Surgery*, *138*(6), 805–806.

Ege, M. J., Mayer, M., Normand, A.-C., Genuneit, J., Cookson, W. O. C. M., Braun-Fahrländer, C., … GABRIELA Transregio 22 Study Group. (2011). Exposure to environmental microorganisms and childhood asthma. *The New England Journal of Medicine*, *364*(8), 701–709. https://doi.org/10.1056/NEJMoa1007302.

El-Kersh, K., Gauhar, U., Cavallazzi, R., & Perez, R. (2014). Inspiratory and Expiratory Vocal Cord Dysfunction: An Upper Airway Obstruction With a Unique Morphological and Quantitative Diagnostic Criteria. *Chest*, *146*(4_MeetingAbstracts), 344A–344A.

Ellis, L. K., & Rothbart, M. K. (1999). Early adolescent temperament questionnaire-revised. *Available from Mary Rothbart, University of Oregon, Maryroth@ OREGON. UOREGON. EDU*.

England, S. J., & Bartlett Jr, D. (1982). Changes in respiratory movements of the human vocal cords during hyperpnea. *Journal of Applied Physiology*, *52*(3), 780–785.

England, SANDRA J., Ho, V., & Zamel, N. (1985). Laryngeal constriction in normal humans during experimentally induced bronchoconstriction. *Journal of Applied Physiology*, *58*(2), 352–356.

Erhardt, W., Hebestedt, A., Aschenbrenner, G., Pichotka, B., & Blümel, G. (1984). A comparative study with various anesthetics in mice (pentobarbitone, ketamine-xylazine, carfentanyl-etomidate). *Research in Experimental Medicine*, *184*(3), 159–169. https://doi.org/10.1007/BF01852390.

Eryonucu, B., Bilge, M., Güler, N., & Uygan, I. (2000). The effect of autonomic nervous system activity on exaggerated blood pressure response to exercise: evaluation by heart rate variability. *Acta Cardiologica*, *55*(3), 181–185.

Fallon, K. E. (2004). Upper airway obstruction masquerading as exercise induced bronchospasm in an elite road cyclist. *British Journal of Sports Medicine*, *38*(4), e9–e9.

Ferris, R. L., Eisele, D. W., & Tunkel, D. E. (1998). Functional laryngeal dyskinesia in children and adults. *The Laryngoscope*, *108*(10), 1520–1523.

Fink, B. R. (1956). The etiology and treatment of laryngeal spasm. *Anesthesiology*, *17*(4), 569–577.

Fitch, W. T., & Giedd, J. (1999). Morphology and development of the human vocal tract: A study using magnetic resonance imaging. *The Journal of the Acoustical Society of America*, *106*, 1511.

Fliege, H., Grimm, A., Eckhardt-Henn, A., Gieler, U., Martin, K., & Klapp, B. F. (2007). Frequency of ICD-10 factitious disorder: survey of senior hospital consultants and physicians in private practice. *Psychosomatics*, *48*(1), 60–64.

Foglio, K., Bianchi, L., Bruletti, G., Battista, L., Pagani, M., & Ambrosino, N. (1999). Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *European Respiratory Journal*, *13*(1), 125–132.

Fontana, G. A., & Lavorini, F. (2006). Cough motor mechanisms. *Respiratory Physiology & Neurobiology*, *152*(3), 266–281.

Forrest, L. A., Husein, T., & Husein, O. (2012). Paradoxical vocal cord motion: classification and treatment. *The Laryngoscope*, *122*(4), 844–853. https://doi.org/10.1002/lary.23176.

Fowler, S. J., Gore, R. B., Vyas, A., & Haines, J. (2010). Vocal cord dysfunction presenting only in expiration with normal inspiratory vocal cord movement. *Am J Respir Crit Care Med*, *181*, A2757.

Freedman, M. R., Rosenberg, S. J., & Schmaling, K. B. (1991). Childhood sexual abuse in patients with paradoxical vocal cord dysfunction. *The Journal of Nervous and Mental Disease*, *179*(5), 295–298.

Fritz, G. K., Fritsch, S., & Hagino, O. (1997). Somatoform disorders in children and adolescents: a review of the past 10 years. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(10), 1329–1338.

Gallena, S. J., Tian, W., Johnson, A. T., Vossoughi, J., Sarles, S. A., & Solomon, N. P. (2013). Validity of a New Respiratory Resistance Measurement Device to Detect Glottal Area Change. *Journal of Voice*, *27*(3), 299–304.

Gallivan, G. J. (2001). Paradoxical Vocal Cord Movement Paradoxical Vocal Cord Movement. *Chest*, *119*(5), 1619–1620.

Gallivan, G. J., Hoffman, L., & Gallivan, K. H. (1996). Episodic paroxysmal laryngospasm: voice and pulmonary function assessment and management. *Journal of Voice*, *10*(1), 93–105.

Gardner, W. N. (1996). The pathophysiology of hyperventilation disorders. *Chest Journal*, *109*(2), 516–534.

Garssen, B., de Ruiter, C., & Van Dyck, R. (1992). Breathing retraining: A rational placebo? *Clinical Psychology Review*, *12*(2), 141–153.

Gartner-Schmidt, J. L., Shembel, A. C., Zullo, T. G., & Rosen, C. A. (2014). Development and Validation of the Dyspnea Index (DI): A Severity Index for Upper Airway–Related Dyspnea. *Journal of Voice*, *28*(6), 775–782. https://doi.org/10.1016/j.jvoice.2013.12.017

Gavin, L. A., Wamboldt, M., Brugman, S. M., Roesler, T. A., & Wamboldt, F. (1998). Psychological and family characteristics of adolescents with vocal cord dysfunction. *Journal of Asthma*, *35*(5), 409–417.

Gaziano, J., & Serrano, J. I. (2012). Transferable skills in the field of speech language pathology. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *20*(3), 155–159. https://doi.org/10.1097/MOO.0b013e3283534e9b

Getty, R. S. (1975). Grossman's the anatomy of the domestic animals. *Vol. I, 5th Ed. Philadelphia, WB Saunders Co.*

Gibson, P. G., & Vertigan, A. E. (2009). Speech pathology for chronic cough: a new approach. *Pulmonary Pharmacology & Therapeutics*, *22*(2), 159–162.

Gillespie, A. I., Dastolfo, C., Magid, N., & Gartner-Schmidt, J. (2014). Acoustic analysis of four common voice diagnoses: moving toward disorder-specific assessment. *Journal of Voice: Official Journal of the Voice Foundation*, *28*(5), 582–588. https://doi.org/10.1016/j.jvoice.2014.02.002

Gillespie, A. I., Gartner-Schmidt, J., Rubinstein, E. N., & Abbott, K. V. (2013). Aerodynamic profiles of women with muscle tension dysphonia/aphonia. *Journal of Speech, Language, and Hearing Research*, *56*(2), 481–488.

Gimenez, L. M., & Zafra, H. (2011). Vocal cord dysfunction: an update. *Annals of Allergy, Asthma & Immunology*, *106*(4), 267–274.

Gordon, G. H. (1987). Treating somatizing patients. *The Western Journal of Medicine*, *147*(1), 88–91.

Gozal, D., Omidvar, O., Kirlew, K. A., Hathout, G. M., Lufkin, R. B., & Harper, R. M. (1996). Functional magnetic resonance imaging reveals brain regions mediating the response to resistive expiratory loads in humans. *Journal of Clinical Investigation*, *97*(1), 47.

Grant, B. F., Hasin, D. S., Stinson, F. S., Dawson, D. A., Chou, S. P., Ruan, W. J., & Pickering, R. P. (2004). Prevalence, Correlates, and Disability of Personality Disorders in the United States: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of Clinical Psychiatry*, *65*(7), 948–958.

Greenberger, P. A., & Grammer, L. C. (2010). Pulmonary disorders, including vocal cord dysfunction. *Journal of Allergy and Clinical Immunology*, *125*(2), S248–S254.

Guglani, L., Atkinson, S., Hosanagar, A., & Guglani, L. (2014). A systematic review of psychological interventions for adult and pediatric patients with vocal cord dysfunction. *Frontiers in Pediatrics*, *2*, 82. https://doi.org/10.3389/fped.2014.00082

Guidelines for the diagnosis and management of asthma (1991). National Asthma Education Program, Office of Prevention, Education, and Control, National Heart, Lung, and Blood Institute, National Institutes of Health.

Guss, J., & Mirza, N. (2006). Methacholine challenge testing in the diagnosis of paradoxical vocal fold motion. *The Laryngoscope*, *116*(9), 1558–1561. https://doi.org/10.1097/01.mlg.0000228007.74561.33

Hammer, M. J., & Krueger, M. A. (2013). Voice-related modulation of mechanosensory detection thresholds in the human larynx. *Experimental Brain Research*, *232*(1), 13–20. https://doi.org/10.1007/s00221-013-3703-1

Han, J. N., Stegen, K., De Valck, C., Clement, J., & Van de Woestijne, K. P. (1996). Influence of breathing therapy on complaints, anxiety and breathing pattern in patients with hyperventilation syndrome and anxiety disorders. *Journal of Psychosomatic Research*, *41*(5), 481–493.

Harms, C. A., Wetter, T. J., Croix, C. M. S., Pegelow, D. F., & Dempsey, J. A. (2000). Effects of respiratory muscle work on exercise performance. *Journal of Applied Physiology*, *89*(1), 131–138.

Hatzelis, V., & Murry, T. (2012). Paradoxical vocal fold motion: respiratory retraining to manage long-term symptoms. *Jornal Da Sociedade Brasileira de Fonoaudiologia*, *24*(1), 80–85.

Heatley, D. G., & Swift, E. (1996). Paradoxical vocal cord dysfunction in an infant with stridor and gastroesophageal reflux. *International Journal of Pediatric Otorhinolaryngology*, *34*(1), 149–151.

Heimdal, J. H., Roksund, O. D., Halvorsen, T., Skadberg, B. T., & Olofsson, J. (2006). Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise. *The Laryngoscope*, *116*(1), 52–57.

Heinle, R., Linton, A., & Chidekel, A. S. (2003). Exercise-induced vocal cord dysfunction presenting as asthma in pediatric patients: toxicity of inappropriate inhaled corticosteroids and the role of exercise laryngoscopy. *Pediatric Asthma, Allergy & Immunology*, *16*(4), 215–224.

Helou, L. B. (2014). *Intrinsic laryngeal muscle response to a speech preparation stressor: Personality and autonomic predictors*. University of Pittsburgh. Retrieved from http://d-scholarship.pitt.edu/21069/1/Helou_Dissertation_ETD_5May2014_CURRENT.pdf

Helou, L. B., Wang, W., Ashmore, R. C., Rosen, C. A., & Abbott, K. V. (2013). Intrinsic laryngeal muscle activity in response to autonomic nervous system activation. *The Laryngoscope*, *123*(11), 2756–2765.

Herin, F., Poussel, M., Renaudin, J. M., Leininger, A., Moreau-Colson, C., Menard, O., & Paris, C. (2012). A 38-year-old hairdresser with irritant-associated vocal cord dysfunction [Case study]. *The International Journal of Tuberculosis and Lung Disease*, *16*(1), 138–139.

Hicks, M., Brugman, S. M., & Katial, R. (2008). Vocal cord dysfunction/paradoxical vocal fold motion. *Primary Care: Clinics in Office Practice*, *35*(1), 81–103.

Higenbottam, T. (1980). Narrowing of glottis opening in humans associated with experimentally induced bronchoconstriction. *Journal of Applied Physiology*, *49*(3), 403–407.

Hill, A. P., & Madigan, D. J. (2017). A short review of perfectionism in sport, dance and exercise: out with the old, in with the 2×2. *Current Opinion in Psychology*, *16*(Supplement C), 72–77. https://doi.org/10.1016/j.copsyc.2017.04.021

Hillel, A. D. (2001). The Study of Laryngeal Muscle Activity in Normal Human Subjects and in Patients With Laryngeal Dystonia Using Multiple Fine-Wire Electromyography. *The Laryngoscope*, *111*(S97), 1–47.

Hillman, R. (2004). Improving the Assessment and Treatment of Voice Disorders: Emerging Technologies. *Proceedings of From Sound to Sense 2004*. Retrieved from http://www.rle.mit.edu/soundtosense/conference/pdfs/invitedspeakers/Hillman%20PAPER.pdf

Hillman, R. E., Holmberg, E. B., Perkell, J. S., Walsh, M., & Vaughan, C. (1989). Objective assessment of vocal hyperfunction: an experimental framework and initial results. *Journal of Speech and Hearing Research*, *32*(2), 373–392.

Hixon, T. J., & Putnam, A. H. B. (1983). Voice disorders in relation to respiratory kinematics. In *Seminars in Speech and Language* (Vol. 4, pp. 217–231).

Hlastala, M. P., & Berger, A. J. (2001). *Physiology of respiration*. Oxford University Press. Retrieved from http://books.google.com/books?hl=en&lr=&id=BmVFS2oEZWQC&oi=fnd&pg=PP2&dq=hlastala+and+berger+physiology+of+respiration&ots=UjhMaSfr4Y&sig=uAUzbvgqMGmVnxPeZdEWiA6ErlY

Holmes, P. W., Lau, K. K., Crossett, M., Low, C., Buchanan, D., Hamilton, G. S., & Bardin, P. G. (2009). Diagnosis of vocal cord dysfunction in asthma with high resolution dynamic volume computerized tomography of the larynx. *Respirology*, *14*(8), 1106–1113.

Hoyte, F. C. (2013). Vocal cord dysfunction. *Immunology and Allergy Clinics of North America*, *33*(1), 1–22.

Hu, Z.W., Wang, Z.-G., Zhang, Y., Tian, S.-R., Wu, J.-M., Zhu, G.-C., & Liang, W.-T. (2014). Gastroesophageal reflux in chronic cough and cough syncope and the effect of antireflux treatment: case report and literature review. *The Annals of Otology, Rhinology, and Laryngology*, *123*(10), 719–725. https://doi.org/10.1177/0003489414534011

Hudgins, P. A., Siegel, J., Jacobs, I., & Abramowsky, C. R. (1997). The normal pediatric larynx on CT and MR. *AJNR. American Journal of Neuroradiology*, *18*(2), 239–245.

Hurbis, C. G., Schild, J. A., & others. (1991). Laryngeal changes during exercise and exercise-induced asthma. *The Annals of Otology, Rhinology, and Laryngology*, *100*(1), 34.

Husein, O. F., Husein, T. N., Gardner, R., Chiang, T., Larson, D. G., Obert, K., … Forrest, L. A. (2008). Formal psychological testing in patients with paradoxical vocal fold dysfunction. *The Laryngoscope*, *118*(4), 740–747.

Ibrahim, W. H., Gheriani, H. A., Almohamed, A. A., & Raza, T. (2007). Paradoxical vocal cord motion disorder: past, present and future. *Postgraduate Medical Journal*, *83*(977), 164–172.

Intarakamhang, P., & Wangjongmeechaikul, P. (2013). The Assessment of Dyspnea during the Vigorous Intensity Exercise by Three Dyspnea Rating Scales in Inactive Medical Personnel. *Global Journal of Health Science*, *5*(6), 19–29. https://doi.org/10.5539/gjhs.v5n6p19

Irwin, R. S., Curley, F. J., & French, C. L. (1990). Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *American Review of Respiratory Disease*, *141*(3), 640–647.

Ishman, S. L., Martin, T. J., Hambrook, D. W., Smith, T. L., Jaradeh, S. S., & Loehrl, T. A. (2007). Autonomic nervous system evaluation in allergic rhinitis. *Otolaryngology–Head and Neck Surgery*, *136*(1), 51–56.

Jacobson, B. H., Johnson, A., Grywalski, C., Silbergleit, A., Jacobson, G., Benninger, M. S., & Newman, C. W. (1997). The voice handicap index (VHI): development and validation. *American Journal of Speech-Language Pathology*, *6*(3), 66.

Jain, S., Bandi, V., Officer, T., Wolley, M., & Guntupalli, K. K. (2006). Role of vocal cord function and dysfunction in patients presenting with symptoms of acute asthma exacerbation. *Journal of Asthma*, *43*(3), 207–212.

Jamilla, F., Stevens, D., & Szidon, P. (2000). Vocal cord dysfunction. *Clinical Pulmonary Medicine*, *7*(3), 111–119.

Jaradeh, S. S., Smith, T. L., Torrico, L., Prieto, T. E., Loehrl, T. A., Darling, R. J., & Toohill, R. J. (2000). Autonomic nervous system evaluation of patients with vasomotor rhinitis. *The Laryngoscope*, *110*(11), 1828–1831.

Johansson, E.L. (2013). Airway reactions and breathing movements in sensory hyperreactivity. Retrieved from https://gupea.ub.gu.se/handle/2077/31722

Johansson, H., Norlander, K., Berglund, L., Janson, C., Malinovschi, A., Nordvall, L., … Emtner, M. (2015). Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. *Thorax*, *70*(1), 57–63.

Jones, M., Harvey, A., Marston, L., & O'Connell, N. E. (2013). Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults. *Cochrane Database of Systematic Reviews*.

Kalk, N. J., Nutt, D. J., & Lingford-Hughes, A. R. (2011). The role of central noradrenergic dysregulation in anxiety disorders: evidence from clinical studies. *Journal of Psychopharmacology*, *25*(1), 3–16.

Karlsson, J. A. (1994). Excitatory nonadrenergic, noncholinergic innervation of airways smooth muscle: Roles of peptides. In *Airways Smooth Muscle*. Switzerland: Birkhauser Verlag Beasel.

Kaufman, K. R., Mohebati, A., & Sotolongo, A. (2004). Pseudoseizures and hysterical stridor. *Epilepsy & Behavior*, *5*(2), 269–272.

Kenn, K, & Balkissoon, R. (2011). Vocal cord dysfunction: what do we know? *The European Respiratory Journal*, *37*(1), 194–200. https://doi.org/10.1183/09031936.00192809

Kenn, Klaus, & Hess, M. M. (2008). Vocal cord dysfunction: an important differential diagnosis of bronchial asthma. *Deutsches Arzteblatt International*, *105*(41), 699.

Kivity, S., Bibi, H., Schwarz, Y., Greif, Y., Topilsky, M., & Tabachnick, E. (1986). Variable vocal cord dysfunction presenting as wheezing and exercise-induced asthma. *Journal of Asthma*, *23*(5), 241–244.

Klahn, M. S., & Perlman, A. L. (1999). Temporal and durational patterns associating respiration and swallowing. *Dysphagia*, *14*(3), 131–138.

Koufman, & Block. (2008). Differential diagnosis of paradoxical vocal fold movement. *American Journal of Speech-Language Pathology*, *17*(4), 327.

Koufman, J. A., & Blalock, P. D. (1982). Classification and approach to patients with functional voice disorders. *The Annals of Otology, Rhinology, and Laryngology*, *91*(4 Pt 1), 372.

Kreher, J. B., & Schwartz, J. B. (2012). Overtraining Syndrome. *Sports Health*, *4*(2), 128–138. https://doi.org/10.1177/1941738111434406

Krouse, J. H., Veling, M. C., Ryan, M. W., Pillsbury, H. C., Krouse, H. J., Joe, S., … Brown, R. W. (2007). Executive summary: asthma and the unified airway. *Otolaryngology–Head and Neck Surgery*, *136*(5), 699–706.

Kuppersmith, R., Rosen, D. S., & Wiatrak, B. J. (1993). Functional stridor in adolescents. *Journal of Adolescent Health*, *14*(3), 166–171.

Lacy, T. J., & McManis, S. E. (1994). Psychogenic stridor. *General Hospital Psychiatry*, *16*(3), 213–223.

Landwehr, L. P., Wood II, R. P., Blager, F. B., & Milgrom, H. (1996). Vocal cord dysfunction mimicking exercise-induced bronchospasm in adolescents. *Pediatrics*, *98*(5), 971–974.

Langdeau, J. B., Turcotte, H., Desagné, P., Jobin, J., & Boulet, L. P. (2000). Influence of sympatho-vagal balance on airway responsiveness in athletes. *European Journal of Applied Physiology*, *83*(4–5), 370–375.

Lehmann, M., Foster, C., Dickhuth, H. H., & Gastmann, U. (1998). Autonomic imbalance hypothesis and overtraining syndrome. *Medicine and Science in Sports and Exercise*, *30*(7), 1140–1145. https://doi.org/10.1097/00005768-199807000-00019

Leo, R. J., & Konakanchi, R. (1999). Psychogenic respiratory distress: a case of paradoxical vocal cord dysfunction and literature review. *Primary Care Companion to the Journal of Clinical Psychiatry*, *1*(2), 39.

Ley, R. (1985). Agoraphobia, the panic attack and the hyperventilation syndrome. *Behaviour Research and Therapy*, *23*(1), 79–81.

Lichstein, P. R. (1986). Caring for the patient with multiple somatic complaints. *Southern Medical Journal*, *79*(3), 310–314.

Liistro, G., Stănescu, D., Dejonckere, P., Rodenstein, D., & Veriter, C. (1990). Exercise-induced laryngospasm of emotional origin. *Pediatric Pulmonology*, *8*(1), 58–60.

Lima, R. (2012). Vocal cord dysfunction: a frequently forgotten entity. *Case Reports in Pulmonology*, *2012*. Retrieved from http://www.hindawi.com/crim/pulmonology/2012/525493/

Loehrl, T. A., Smith, T. L., Darling, R. J., Torrico, L., Prieto, T. E., Shaker, R., … Jaradeh, S. S. (2002). Autonomic dysfunction, vasomotor rhinitis, and extraesophageal manifestations of gastroesophageal reflux. *Otolaryngology–Head and Neck Surgery*, *126*(4), 382–387.

Loughlin, C. J., & Koufman, J. A. (1996). Paroxysmal laryngospasm secondary to gastroesophageal reflux. *The Laryngoscope*, *106*(12), 1502–1505.

Low, K., Lau, K. K., Holmes, P., Crossett, M., Vallance, N., Phyland, D., … Bardin, P. G. (2011). Abnormal vocal cord function in difficult-to-treat asthma. *American Journal of Respiratory and Critical Care Medicine*, *184*(1), 50–56.

Luecke, T., & Pelosi, P. (2005). Clinical review: Positive end-expiratory pressure and cardiac output. *Critical Care*, *9*(6), 607–621. https://doi.org/10.1186/cc3877

Lum, L. C. (1983). Physiological considerations in the treatment of hyperventilation syndromes. *Journal of Drug Research*, *8*(6), 1867–1872.

Lund, D. S., Garmel, G. M., Kaplan, G. S., & Tom, P. A. (1993). Hysterical stridor: a diagnosis of exclusion. *The American Journal of Emergency Medicine*, *11*(4), 400–402.

Maat, R. C. (2011). Exercise-induced laryngeal obstruction. Diagnostic procedures and therapy.

Maat, R. C, Hilland, M., Røksund, O. D., Halvorsen, T., Olofsson, J., Aarstad, H. J., & Heimdal, J.-H. (2011). Exercise-induced laryngeal obstruction: natural history and effect of surgical treatment. *European Archives of Oto-Rhino-Laryngology*, *268*(10), 1485–1492.

Maat, Robert C., Roksund, O. D., Olofsson, J., Halvorsen, T., Skadberg, B. T., & Heimdal, J.-H. (2007). Surgical treatment of exercise-induced laryngeal dysfunction. *European Archives of Oto-Rhino-Laryngology*, *264*(4), 401–407.

Maat, Røksund, Halvorsen, Skadberg, Olofsson, Ellingsen, … Heimdal. (2009). Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations. *European Archives of Oto-Rhino-Laryngology*, *266*(12), 1929–1936.

MacConnell, L. S., Danielsen, R. D., & Symington, S. (2014). Vocal Cord Dysfunction: Unmasking the asthma pretender. *Clinical Reviews*.

Macey, P. M., Macey, K. E., Henderson, L. A., Alger, J. R., Frysinger, R. C., Woo, M. A., … Harper, R. M. (2003). Functional magnetic resonance imaging responses to expiratory loading in obstructive sleep apnea. *Respiratory Physiology & Neurobiology*, *138*(2), 275–290.

Macklem, P. T., Cohen, C., Zagelbaum, G., & Roussos, C. (1981). The pathophysiology of inspiratory muscle fatigue. *Ciba Foundation Symposium*, *82*, 249–263.

Macklem, P. T., & Roussos, C. S. (1977). Respiratory muscle fatigue: a cause of respiratory failure? *Clinical Science and Molecular Medicine*, *53*(5), 419–422.

Mador, M. J., & Acevedo, F. A. (1991). Effect of Respiratory Muscle Fatigue on Breathing Pattern During Incremental Exercise. *American Review of Respiratory Disease*, *143*(3), 462–468. https://doi.org/10.1164/ajrccm/143.3.462

Martin, R. J., Blager, F. B., Gay, M. L., & Wood, R. P. (1987). Paradoxic vocal cord motion in presumed asthmatics. In *Seminars in Respiratory Medicine* (Vol. 8, pp. 332–337).

Martinez, F. J., de Oca, M. M., Whyte, R. I., Stetz, J., Gay, S. E., & Celli, B. R. (1997). Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *American Journal of Respiratory and Critical Care Medicine*, *155*(6), 1984–1990.

Martínez-Lavín, M., & Hermosillo, A. G. (2000). Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. In *Seminars in arthritis and rheumatism* (Vol. 29, pp. 197–199).

Maschka, D. A., Bauman, N. M., McCray, P. B., Hoffman, H. T., Karnell, M. P., & Smith, R. J. (1997). A classification scheme for paradoxical vocal cord motion. *The Laryngoscope*, *107*(11), 1429–1435.

Mathers-Schmidt, B. A. (2001). Paradoxical vocal fold motion: a tutorial on a complex disorder and the speech-language pathologist's role. *American Journal of Speech Language Pathology*, *10*(2), 111–125.

Mathew, O. P., & Sant'Ambrogio, G. (1988). *Respiratory function of the upper airway* (Vol. 35). New York, New York: Marcel Dekker, Inc.

Matrka, L. (2014). Paradoxic vocal fold movement disorder. *Otolaryngologic Clinics of North America*, *47*(1), 135–146. https://doi.org/10.1016/j.otc.2013.08.014

McArdle, W.D. (n.d.). *Exercise physiology: nutrition, energy, and human performance*.

McConnell, A. K., & Romer, L. M. (2004). Respiratory Muscle Training in Healthy Humans: Resolving the Controversy. *International Journal of Sports Medicine*, *25*(04), 284–293. https://doi.org/10.1055/s-2004-815827

McEwen, B. S. (1998). Protective and Damaging Effects of Stress Mediators. *New England Journal of Medicine*, *338*(3), 171–179. https://doi.org/10.1056/NEJM199801153380307

McEwen, B. S. (2000). Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology*, *22*(2), 108–124.

McEwen, B.S. (2007). Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain. *Physiological Reviews*, *87*(3), 873–904. https://doi.org/10.1152/physrev.00041.2006

McFadden Jr, E. R., & Zawadski, D. K. (1996). Vocal cord dysfunction masquerading as exercise-induced asthma. a physiologic cause for“ choking” during athletic activities. *American Journal of Respiratory and Critical Care Medicine*, *153*(3), 942–947.

McGrath, K. G., Greenberger, P. A., Zeiss, C. R., & others. (1984). Factitious allergic disease: multiple factitious illness and familial Munchausen’s stridor. *Immunol Allergy Pract*, *6*(7), 263–71.

McKenna, V. S., Murray, E. S. H., Lien, Y.-A. S., & Stepp, C. E. (2016). The Relationship Between Relative Fundamental Frequency and a Kinematic Estimate of Laryngeal Stiffness in Healthy Adults. *Journal of Speech, Language, and Hearing Research*, *59*(6), 1283–1294. https://doi.org/10.1044/2016_JSLHR-S-15-0406

Medelli, J., Lounana, J., Messan, F., Menuet, J., & Petitjean, M. (2006). Testing of pulmonary function in a professional cycling team. *Journal of Sports Medicine and Physical Fitness*, *46*, 298–306.

Mehta, D. D., & Hillman, R. E. (2008). Voice assessment: updates on perceptual, acoustic, aerodynamic, and endoscopic imaging methods. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *16*(3), 211.

Michoud, M.C. (2005). Neurohumoral control of the airways. *Physiologic Basis of Respiratory Disease*, 363.

Middlekauff, H. R., Park, J., & Moheimani, R. S. (2014). Adverse Effects of Cigarette and Noncigarette Smoke Exposure on the Autonomic Nervous System: Mechanisms and Implications for Cardiovascular Risk. *Journal of the American College of Cardiology*, *64*(16), 1740–1750.

Mikita, J. A., & Mikita, C. P. (2006). Vocal cord dysfunction (Vol. 27, pp. 411–414).

Milgrom, H., Corsello, P., Freedman, M., Blager, F. B., & Wood, R. P. (1990). Differential diagnosis and management of chronic cough. *Comprehensive Therapy*, *16*(10), 46–53.

Minassian, V. A., Drutz, H. P., & Al-Badr, A. (2003). Urinary incontinence as a worldwide problem. *International Journal of Gynecology & Obstetrics*, *82*(3), 327–338. https://doi.org/10.1016/S0020-7292(03)00220-0

Mobeireek, A., Alhamad, A., Al-Subaei, A., & Alzeer, A. (1995). Psychogenic vocal cord dysfunction simulating bronchial asthma. *European Respiratory Journal*, *8*(11), 1978–1981.

Mokoka, M. C., Ullah, K., Curran, D. R., & O’Connor, T. M. (2013). Rare causes of persistent wheeze that mimic poorly controlled asthma. *BMJ Case Reports*, *2013*. https://doi.org/10.1136/bcr-2013-201100

Moore, C. A., Caulfield, T. J., & Green, J. R. (2001). Relative Kinematics of the Rib Cage and Abdomen during Speech and Nonspeech Behaviors of 15-Month-Old Children. *Journal of Speech, Language, and Hearing Research : JSLHR*, *44*(1), 80–94.

Moran, M. G. (1996). Psychiatric aspects of rheumatology. *Psychiatric Clinics of North America*, *19*(3), 575–587. https://doi.org/10.1016/S0193-953X(05)70306-3

Morris, M. J, Allan, P. F., & Perkins, P. J. (2006). Vocal cord dysfunction: etiologies and treatment. *Clinical Pulmonary Medicine*, *13*(2), 73.

Morris, M.J., & Christopher, K. L. (2010). Diagnostic criteria for the classification of vocal cord dysfunction. *Chest*, *138*(5), 1213–1223.

Morris, M.J., Deal, L. E., Bean, D. R., Grbach, V. X., & Morgan, J. A. (1999). Vocal cord dysfunction in patients with exertional dyspnea. *Chest*, *116*(6), 1676–1682.

Morris, M.J., Oleszewski, R. T., Sterner, J. B., & Allan, P. F. (2013). Vocal cord dysfunction related to combat deployment. *Military Medicine*, *178*(11), 1208–1212. https://doi.org/10.7205/MILMED-D-13-00155

Morrison, M.J. & Rammage, L. (2010a). The irritable larynx syndrome as a central sensitivity syndrome. *Canadian Journal of Speech-Language Pathology and Audiology*, *34*(4).

Morrison, M.J., & Rammage, L. (2010b). The Irritable Larynx Syndrome as a Central Sensitivity Syndrome Le syndrome du larynx irritable: un syndrome de sensibilité centrale. *Revue Canadienne D'orthophonie et D'audiologie-Vol*, *34*(4), 282.

Morrison, M.J., Rammage, L., & Emami, A. J. (1999). The irritable larynx syndrome. *Journal of Voice*, *13*(3), 447–455.

Mrazek, D. A. (1992). Psychiatric complications of pediatric asthma. *Annals of Allergy*, *69*(4), 285–290.

Mukhopadhyay, J., Bates, R., Manney, S., & Ayres, J. G. (2007). Changes in vagal tone with posture in asthma are related to changes in ventilatory pattern. *Respiratory Medicine*, *101*(5), 1001–1006.

Muntner P, He J, Cutler JA, Wildman RP, & Whelton PK. (2004). Trends in blood pressure among children and adolescents. *JAMA*, *291*(17), 2107–2113. https://doi.org/10.1001/jama.291.17.2107

Murakami, Y., & Kirchner, J. A. (1972). Mechanical and physiological properties of reflex laryngeal closure. *The Annals of Otology, Rhinology, and Laryngology*, *81*(1), 59.

Murakami, Yasushi, & Kirchner, J. A. (1972). Respiratory movements of the vocal cords. An electromyographic study in the cat. *The Laryngoscope*, *82*(3), 454–467.

Muris, P., & Meesters, C. (2009). Reactive and regulative temperament in youths: Psychometric evaluation of the Early Adolescent Temperament Questionnaire-Revised. *Journal of Psychopathology and Behavioral Assessment*, *31*(1), 7–19.

Murry, T., Cukier-Blaj, S., Kelleher, A., & Malki, K. H. (2011). Laryngeal and respiratory patterns in patients with paradoxical vocal fold motion. *Respiratory Medicine*, *105*(12), 1891–1895.

Murry, T., & Sapienza, C. (2010). The role of voice therapy in the management of paradoxical vocal fold motion, chronic cough, and laryngospasm. *Otolaryngologic Clinics of North America*, *43*(1), 73–83.

Nacci, A., Fattori, B., Segnini, G., Dallan, I., Panicucci, E., Rocchi, V., & Ursino, F. (2010). Respiratory retraining therapy in long-term treatment of paradoxical vocal fold dysfunction. *Folia Phoniatrica et Logopaedica*, *63*(3), 134–141.

Nagai, A., Yamaguchi, E., Sakamoto, K., & Takahashi, E. (1992). Functional upper airway obstruction. Psychogenic pharyngeal constriction. *Chest*, *101*(5), 1460–1461.

Nagai, Atsushi, Kanemura, T., & Konno, K. (1992). Abnormal movement of the arytenoid region as a cause of upper airway obstruction. *Thorax*, *47*(10), 840–841.

Nahmias, J., Tansey, M., & Karetzky, M. S. (1994). Asthmatic extrathoracic upper airway obstruction: Laryngeal dyskinesis. *New Jersey Medicine*, *91*(9), 616–622.

Nascimento, T., Tenenbaum, G., & others. (2013). The Psychological Experience of Athletes With Vocal Cord Dysfunction. *Journal of Clinical Sport Psychology*, *7*(2), 146–160.

Nayar, R. C., Zanak, S. R., & Ahmed, S. M. (2003). Hysterical stridor: a report of two cases. *Ear, Nose, & Throat Journal*, *82*(1), 46–48.

Newman, K. B., Mason, U. G., & Schmaling, K. B. (1995). Clinical features of vocal cord dysfunction. *American Journal of Respiratory and Critical Care Medicine*, *152*(4), 1382–1386.

Newman, Kenneth B. (2003). Vocal cord dysfunction. In *Upper and lower respiratory disease* (Vol. 81, pp. 417–427). New York, New York: Marcel Dekker, Inc.

Newman, Kenneth B., & Dubester, S. N. (1994). Vocal cord dysfunction: masquerader of asthma. In *Seminars in respiratory and critical care medicine* (Vol. 15, pp. 161–167). Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=4271815

Nielsen, Emil W., Hull, J., & Backer, V. (2013). High prevalence of exercise-induced laryngeal obstruction in athletes with respiratory symptoms. *European Respiratory Journal*, *42*(Suppl 57), 356.

Nielsen, Emil Walsted, Hull, J. H., & Backer, V. (2013). High prevalence of exercise-induced laryngeal obstruction in athletes. *Medicine and Science in Sports and Exercise*. Retrieved

from http://www.researchgate.net/publication/236665350_High_Prevalence_of_Exercise-Induced_Laryngeal_Obstruction_in_Athletes

Niggemann, B. (2010). How to diagnose psychogenic and functional breathing disorders in children and adolescents. *Pediatric Allergy and Immunology*, *21*(6), 895–899.

Niggemann, B., Paul, K., Keitzer, R., & Wahn, U. (1998). Vocal cord dysfunction in three children-misdiagnosis of bronchial asthma? *Pediatric Allergy and Immunology*, *9*(2), 97–100.

Niven, R. M., Roberts, T., Pickering, C. a. C., & Webb, A. K. (1992). Functional upper airways obstruction presenting as asthma. *Respiratory Medicine*, *86*(6), 513–516. https://doi.org/10.1016/S0954-6111(96)80013-8

Noback, C. R., Strominger, N. L., Demarest, R. J., & Ruggiero, D. A. (2005). *The human nervous system: structure and function*. Springer. Retrieved from http://books.google.com/books?hl=en&lr=&id=eaZtFUdVHqQC&oi=fnd&pg=PA1&dq=noback+human+nervous+system&ots=ju-K-AHXFF&sig=i84MNlWQMiDMgPiIS-jYD6ybaFU

Noyes, B. E., & Kemp, J. S. (2007). Vocal cord dysfunction in children. *Paediatric Respiratory Reviews*, *8*(2), 155–163.

O'Donnell, D. E., Sanii, R., Anthonisen, N. R., & Younes, M. (1987). Effect of dynamic airway compression on breathing pattern and respiratory sensation in severe chronic obstructive pulmonary disease. *The American Review of Respiratory Disease*, *135*(4), 912–918.

Olin, J. Tod, Clary, M. S., Connors, D., Abbott, J., Brugman, S. M., Deng, Y., … Courey, M. (2014). Glottic configuration in patients with exercise-induced stridor: A new paradigm. *The Laryngoscope*, *124*(11), 2568–2573.

Olin, J. Tod, Clary, M. S., Fan, E. M., Johnston, K. L., Strand, M., Christopher, K. L., & others. (2016). Continuous laryngoscopy quantitates laryngeal behaviour in exercise and recovery. *European Respiratory Journal*, ERJ–00160.

Olin, James Tod, Clary, M. S., Deardorff, E. H., Johnston, K., Morris, M. J., Sokoya, M., … Christopher, K. L. (2015). Inducible laryngeal obstruction during exercise: moving beyond vocal cords with new insights. *The Physician and Sportsmedicine*, *43*(1), 13–21. https://doi.org/10.1080/00913847.2015.1007026

Olivier, C. E., Argentão, D. G. P., Lima, R. P. dos S., da Silva, M. D., & dos Santos, R. A. P. G. (2013). The nasal provocation test combined with spirometry establishes paradoxical vocal fold motion in allergic subjects. *Allergy and Asthma Proceedings: The Official Journal of Regional and State Allergy Societies*, *34*(5), 453–458. https://doi.org/10.2500/aap.2013.34.3681

Opolski, M., & Wilson, I. (2005). Asthma and depression: a pragmatic review of the literature and recommendations for future research. *Clinical Practice and Epidemiology in Mental Health*, *1*(1), 18.

Orenstein, S. R. (2001). An overview of reflux-associated disorders in infants: apnea, laryngospasm, and aspiration. *The American Journal of Medicine*, *111*(8), 60–63.

Oyama, O. (2011). Somatoform Disorders–November 1, 2007–American Family Physician. *Website–American Academy of Family Physicians. Web*, *30*.

Paridon, S. M., Alpert, B. S., Boas, S. R., Cabrera, M. E., Caldarera, L. L., Daniels, S. R., … Yetman, A. T. (2006). Clinical Stress Testing in the Pediatric Age Group A Statement From the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. *Circulation*, *113*(15), 1905–1920. https://doi.org/10.1161/CIRCULATIONAHA.106.174375

Parshall, M. B., Schwartzstein, R. M., Adams, L., Banzett, R. B., Manning, H. L., Bourbeau, J., … Lareau, S. C. (2012). An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *American Journal of Respiratory and Critical Care Medicine*, *185*(4). Retrieved from http://www.atsjournals.org/doi/abs/10.1164/rccm.201111-2042ST

Parsons, J. P., Benninger, C., Hawley, M. P., Philips, G., Forrest, L. A., & Mastronarde, J. G. (2010). Vocal cord dysfunction: beyond severe asthma. *Respiratory Medicine*, *104*(4), 504–509.

Patterson, D. L., & O'Connell, E. J. (1994). Vocal cord dysfunction: what have we learned in 150 years. *Insights Allergy*, *9*(6), 1–12.

Patterson, R., Schatz, M., & Horton, M. (1974). Munchausen's stridor: non-organic laryngeal obstruction. *Clinical & Experimental Allergy*, *4*(3), 307–310.

Pediatric Blood Pressure Reference. (n.d.). Retrieved February 18, 2016, from https://www.bcm.edu/bodycomplab/Flashapps/BPVAgeChartpage.html

Perkins, M. A. J. P. ., & Morris, L. T. C. M. . (2002). Vocal Cord Dysfunction Induced by Methacholine Challenge Testing. *Chest*, *122*(6), 1988–1993.

Perkner, J. J., Fennelly, K. P., Balkissoon, R., Bartelson, B. B., Ruttenber, A. J., Wood, R. P., & Newman, L. S. (1998). Irritant-associated vocal cord dysfunction. *Journal of Occupational and Environmental Medicine*, *40*(2), 136–143.

Pierpont, G. L., & Voth, E. J. (2004). Assessing autonomic function by analysis of heart rate recovery from exercise in healthy subjects. *The American Journal of Cardiology*, *94*(1), 64–68.

Pinho, S. M., Tsuji, D. H., Sennes, L., & Menezes, M. (1997). Paradoxical vocal fold movement: a case report. *Journal of Voice*, *11*(3), 368–372.

Pitchenik, A. E. (1991). Functional laryngeal obstruction relieved by panting. *Chest*, *100*(5), 1465–1467.

Pollock, M. L., Wilmore, J. H., & Fox, S. S. M. (1984). *Exercise in health and disease: evaluation and prescription for prevention and rehabilitation*. Saunders.

Powell, D. M., Karanfilov, B. I., Beechler, K. B., Treole, K., Trudeau, M. D., & Forrest, L. A. (2000). Paradoxical vocal cord dysfunction in juveniles. *Archives of Otolaryngology—Head & Neck Surgery*, *126*(1), 29.

Puetz, T. R., & Vakil, N. (1995). Gastroesophageal reflux-induced cough syncope. *The American Journal of Gastroenterology*, *90*(12), 2204–2206.

Rafael, E., Shohet, M. R., & Cohen, J. M. (2010). Occupational rhinosinusitis and upper airway disease: the world trade center experience. *Current Allergy and Asthma Reports*, *10*(2), 77–83.

Rajakulasingam, K., & Durham, S. R. (2003). Comparative Pathogenesis of Upper and Lower Airway Allergic Disease. *Lung Biology in Health and Disease*, *181*, 139–157.

Reid, W. D., & MacGowan, N. A. (1998). Respiratory muscle injury in animal models and humans. *Molecular and Cellular Biochemistry*, *179*(1–2), 63–80. https://doi.org/10.1023/A:1006803703128

Reidenbach, M. M. (1998). Aryepiglottic fold: normal topography and clinical implications. *Clinical Anatomy*, *11*(4), 223–235.

Rhodes, R. K. (2008). Diagnosing vocal cord dysfunction in young athletes. *Journal of the American Academy of Nurse Practitioners*, *20*(12), 608–613.

Richards-Mauzé, M. M., & Banez, G. A. (2014). Vocal cord dysfunction: Evaluation of a four-session cognitive–behavioral intervention. *Clinical Practice in Pediatric Psychology*, *2*(1), 27.

Ries, A. L. (2005). Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg Scale, and Visual Analog Scale. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *2*(1), 105–110.

Ringsberg, K. C., Löwhagen, O., & Sivik, T. (1993). Psychological differences between asthmatics and patients suffering from an asthma-like condition, functional breathing disorder: A comparison between the two groups concerning personality, psychosocial and somatic parameters. *Integrative Physiological and Behavioral Science*, *28*(4), 358–367. https://doi.org/10.1007/BF02690933

Ritz, T., Steptoe, A., Bobb, C., Harris, A. H., & Edwards, M. (2006). The asthma trigger inventory: validation of a questionnaire for perceived triggers of asthma. *Psychosomatic Medicine*, *68*(6), 956–965.

Rodenstein, D. O., Francis, C., & St\uanescu, D. C. (1983). Emotional laryngeal wheezing: a new syndrome. *The American Review of Respiratory Disease*, *127*(3), 354–356.

Røksund, O. D., Maat, R. C., Heimdal, J. H., Olofsson, J., Skadberg, B. T., & Halvorsen, T. (2009). Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. *Respiratory Medicine*, *103*(12), 1911–1918.

Rolla, G., Colagrande, P., Magnano, M., Debernardi, V., Dutto, L., Delpiano, L., … Bucca, C. (1998). Extrathoracic airway dysfunction in cough associated with gastroesophageal reflux. *Journal of Allergy and Clinical Immunology*, *102*(2), 204–209.

Romer, L. M., McConnell, A. K., & Jones, D. A. (2002). Effects of inspiratory muscle training on time-trial performance in trained cyclists. *Journal of Sports Sciences*, *20*(7), 547–590. https://doi.org/10.1080/026404102760000053

Romer, L. M., & Polkey, M. I. (2008). Exercise-induced respiratory muscle fatigue: implications for performance. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *104*(3), 879–888. https://doi.org/10.1152/japplphysiol.01157.2007

Rosen, C. A., & Murry, T. (2000). Nomenclature of voice disorders and vocal pathology. *Otolaryngologic Clinics of North America*, *33*(5), 1035–1045.

Rosenbek, J. C., Robbins, J. A., Roecker, E. B., Coyle, J. L., & Wood, J. L. (1996). A penetration-aspiration scale. *Dysphagia*, *11*(2), 93–98.

Rothe, T. B., & Karrer, W. (1998). Functional upper airway obstruction and chronic irritation of the larynx. *European Respiratory Journal*, *11*(2), 498–500.

Roy, W. L., & Lerman, J. (1988). Laryngospasm in paediatric anaesthesia. *Canadian Journal of Anaesthesia = Journal Canadien D'anesthésie*, *35*(1), 93–98. https://doi.org/10.1007/BF03010554

Rubin, J. S., Macdonald, I., & Blake, E. (2011). The putative involvement of the transabdominal muscles in dysphonia: A preliminary study and thoughts. *Journal of Voice*, *25*(2), 218–222.

Rundell, K. W., & Spiering, B. A. (2003). Inspiratory Stridor in Elite Athletes. *Chest*, *123*(2), 468–474.

Ryan, N. M., Vertigan, A. E., & Gibson, P. G. (2009). Chronic cough and laryngeal dysfunction improve with specific treatment of cough and paradoxical vocal fold movement. *Cough*, *5*(4). Retrieved from http://www.biomedcentral.com/content/pdf/1745-9974-5-4.pdf

Sandage, M. J., & Zelazny, S. K. (2004). Paradoxical vocal fold motion in children and adolescents. *Language, Speech, and Hearing Services in Schools*, *35*(4), 353.

Sandhu, G. S., & Kuchai, R. (2013). The larynx in cough. *Cough*, *9*(1), 16. https://doi.org/10.1186/1745-9974-9-16

Sapienza, C., Al-Natour, Y., Schmalz, M. S., & Ritter, G. X. (2000). Analysis of error in measuring laryngeal size parameters from compressed imagery. In *International Symposium on Optical Science and Technology* (pp. 101–114). International Society for Optics and Photonics.

Sapienza, C. M., Ruddy, B. H., & Baker, S. (2004). Laryngeal structure and function in the pediatric larynx: clinical applications. *Language, Speech & Hearing Services in Schools*, *35*(4).

Sarafino, E. P., & Goldfedder, J. (1995). Genetic factors in the presence, severity, and triggers of asthma. *Archives of Disease in Childhood*, *73*(2), 112–116.

Sasaki MD, C. T., & Weaver MD, E. M. (1997). Physiology of the larynx. *The American Journal of Medicine*, *103*(5), 9S–18S.

Scano, G., Stendardi, L., & Grazzini, M. (2005). Understanding dyspnoea by its language. *European Respiratory Journal*, *25*(2), 380–385.

Scheinherr, A., Bailly, L., Boiron, O., Lagier, A., Legou, T., Pichelin, M., … Giovanni, A. (2015). Realistic glottal motion and airflow rate during human breathing. *Medical Engineering & Physics*, *37*(9), 829–839. https://doi.org/10.1016/j.medengphy.2015.05.014

Selner, J. C., Staudenmayer, H., Koepke, J. W., Harvey, R., & Christopher, K. (1987). Vocal cord dysfunction: the importance of psychologic factors and provocation challenge testing. *Journal of Allergy and Clinical Immunology*, *79*(5), 726–733.

Shembel, A. C., Kolouri, S., Xu, H., & Verdolini Abbott, K. (2015). Quantification of respiratory laryngeal morphometry: comparison of laryngeal lumen angle estimate methods. *Journal of Voice, Advance online publication*.

Shembel, A. C., Rosen, C. A., Zullo, T. G., & Gartner-Schmidt, J. L. (2013). Development and validation of the cough severity index: a severity index for chronic cough related to the upper airway. *The Laryngoscope*, *123*(8), 1931–1936. https://doi.org/10.1002/lary.23916

Shembel, A. C., Sandage, M. J., & Verdolini Abbott, K. (2017). Episodic Laryngeal Breathing Disorders: Literature review and proposal of preliminary theoretical framework. *Journal of Voice*, *31*(1), 125.e7-125.e16.

Singh, T. P., Rhodes, J., & Gauvreau, K. (2008). Determinants of heart rate recovery following exercise in children. *Medicine and Science in Sports and Exercise*, *40*(4), 601–605. https://doi.org/10.1249/MSS.0b013e3181621ec4

Smith, M. E., Darby, K. P., Kirchner, K., & Blager, F. B. (1993). Simultaneous functional laryngeal stridor and functional aphonia in an adolescent. *American Journal of Otolaryngology*, *14*(5), 366–369.

Smith, M. S. (1983). Acute psychogenic stridor in an adolescent athlete treated with hypnosis. *Pediatrics*, *72*(2), 247–248.

Snyder, H. R., Gulley, L. D., Bijttebier, P., Hartman, C. A., Oldehinkel, A. J., Mezulis, A., … Hankin, B. L. (2015). Adolescent emotionality and effortful control: Core latent constructs and links to psychopathology and functioning. *Journal of Personality and Social Psychology*, *109*(6), 1132–1149. https://doi.org/10.1037/pspp0000047

Snyder, H. S., & Weiss, E. (1989). Hysterical stridor: a benign cause of upper airway obstruction. *Annals of Emergency Medicine*, *18*(9), 991–994.

Sokol, W. (1993). Vocal cord dysfunction presenting as asthma. *Western Journal of Medicine*, *158*(6), 614.

Somers, J. M., Goldner, E. M., Waraich, P., & Hsu, L. (2006). Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, *51*(2), 100–113.

Streeter, C. C., Gerbarg, P. L., Saper, R. B., Ciraulo, D. A., & Brown, R. P. (2012). Effects of yoga on the autonomic nervous system, gamma-aminobutyric-acid, and allostasis in epilepsy, depression, and post-traumatic stress disorder. *Medical Hypotheses*, *78*(5), 571–579.

Sullivan, M. D., Heywood, B. M., & Beukelman, D. R. (2001). A treatment for vocal cord dysfunction in female athletes: an outcome study. *The Laryngoscope*, *111*(10), 1751–1755.

Taramarcaz, P., Grissell, T. V., Borgas, T., & Gibson, P. G. (2004). Transient postviral vocal cord dysfunction. *The Journal of Allergy and Clinical Immunology*, *114*(6), 1471.

Tervonen, H., Niskanen, M. M., Sovijärvi, A. R., Hakulinen, A. S., Vilkman, E. A., & Aaltonen, L.-M. (2009). Fiberoptic videolaryngoscopy during bicycle ergometry: A diagnostic tool for exercise-induced vocal cord dysfunction. *The Laryngoscope*, *119*(9), 1776–1780.

Thach, M. D., & Bradley, T. (1997). Reflux associated apnea in infants: evidence for a laryngeal chemoreflex. *The American Journal of Medicine*, *103*(5), 120S–124S.

Tilles, S. A. (2003). Vocal cord dysfunction in children and adolescents. *Current Allergy and Asthma Reports*, *3*(6), 467–472.

Tilles, Stephen A., & Inglis, A. F. (2009). Masqueraders of exercise-induced vocal cord dysfunction. *Journal of Allergy and Clinical Immunology*, *124*(2), 377–378.

Tonini, S., Dellabianca, A., Costa, C., Lanfranco, A., Scafa, F., & Candura, S. M. (2009). Irritant vocal cord dysfunction and occupational bronchial asthma: differential diagnosis in a health care worker. *International Journal of Occupational Medicine and Environmental Health*, *22*(4), 401–406. https://doi.org/10.2478/v10001-009-0038-z

Traister, R.S., Fajt, M. L., Whitman-Purves, E., Anderson, W. C., & Petrov, A. A. (2013). A retrospective analysis comparing subjects with isolated and coexistent vocal cord dysfunction and asthma. *Allergy and Asthma Proceedings*, *34*(4), 349–355. https://doi.org/10.2500/aap.2013.34.3673

Traister, Russell S., Fajt, M. L., & Petrov, A. A. (2016). The morbidity and cost of vocal cord dysfunction misdiagnosed as asthma. In *Allergy and Asthma Proceedings* (Vol. 37, pp. e25–e31). OceanSide Publications, Inc. Retrieved from http://www.ingentaconnect.com/content/ocean/aap/2016/00000037/00000002/art00002

Treole, K., Trudeau, M. D., & Forrest, L. A. (1999). Endoscopic and stroboscopic description of adults with paradoxical vocal fold dysfunction. *Journal of Voice*, *13*(1), 143–152.

Tunnicliffe, W. S., Hilton, M. F., Harrison, R. M., & Ayres, J. G. (2001). The effect of sulphur dioxide exposure on indices of heart rate variability in normal and asthmatic adults. *The European Respiratory Journal*, *17*(4), 604–608.

Undem, B. J., McAlexander, M., & Hunter, D. D. (1999). Neurobiology of the upper and lower airways. *Allergy*, *54*, 81–93.

Undem, Bradley J., & Potenzieri, C. (2012). Autonomic neural control of intrathoracic airways. *Comprehensive Physiology*. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/cphy.c110032/full

Van den Bergh, O., Van Diest, I., Dupont, L., & Davenport, P. W. (2012). On the psychology of cough. *Lung*, *190*(1), 55–61.

van Dixhoorn, J. (1994). Significance of breathing awareness and exercise training for recovery after myocardial infarction. In *Clinical applied psychophysiology* (pp. 113–132). Springer. Retrieved from http://link.springer.com/chapter/10.1007/978-1-4757-9703-9_9

Vasudev, M. (2012). Evaluation of paradoxical vocal fold motion. *Annals of Allergy, Asthma & Immunology*, *109*(4), 233–236.

Vertigan, A. E, Gibson, P. G., Theodoros, D. G., & Winkworth, A. L. (2007). A review of voice and upper airway function in chronic cough and paradoxical vocal cord movement. *Current Opinion in Allergy and Clinical Immunology*, *7*(1), 37.

Vertigan, A. E, Gibson, P. G., Theodoros, D. G., Winkworth, A. L., Borgas, T., & Reid, C. (2006). Involuntary glottal closure during inspiration in muscle tension dysphonia. *The Laryngoscope*, *116*(4), 643–649.

Vertigan, A. E, Theodoros, D. G., Gibson, P. G., & Winkworth, A. L. (2007). Voice and upper airway symptoms in people with chronic cough and paradoxical vocal fold movement. *Journal of Voice*, *21*(3), 361–383.

Vertigan, A. E, Theodoros, D. G., Winkworth, A. L., & Gibson, P. G. (2008). Acoustic and electroglottographic voice characteristics in chronic cough and paradoxical vocal fold movement. *Folia Phoniatrica et Logopaedica*, *60*(4), 210–216.

Vertigan, Anne E., Bone, S. L., & Gibson, P. G. (2013). Laryngeal sensory dysfunction in laryngeal hypersensitivity syndrome. *Respirology (Carlton, Vic.)*, *18*(6), 948–956. https://doi.org/10.1111/resp.12103

Vertigan, Anne E., Gibson, P. G., Theodoros, D. G., & Winkworth, A. L. (2008). The role of sensory dysfunction in the development of voice disorders, chronic cough and paradoxical vocal fold movement. *International Journal of Speech-Language Pathology*, *10*(4), 231–244. https://doi.org/10.1080/17549500801932089

Vlahakis, N. E., Patel, A. M., Maragos, N. E., & Beck, K. C. (2002). Diagnosis of Vocal Cord DysfunctionThe Utility of Spirometry and Plethysmography. *CHEST Journal*, *122*(6), 2246–2249.

Von Leupoldt, A., Mertz, C., Kegat, S., Burmester, S., & Dahme, B. (2006). The impact of emotions on the sensory and affective dimension of perceived dyspnea. *Psychophysiology*, *43*(4), 382–386.

Walsted, E. S., Swanton, L. L., van van Someren, K., Morris, T. E., Furber, M., Backer, V., & Hull, J. H. (2017). Laryngoscopy during swimming: A novel diagnostic technique to characterize swimming-induced laryngeal obstruction. *The Laryngoscope*, *127*(10), 2298–2301. https://doi.org/10.1002/lary.26532

Wamboldt, F., Balkissoon, R., & Amerigo, P. (2001). Diagnoses associated with persistent shortness of breath and upper airway dysfunction in patients with and without occupational or environmental exposure. *Am J Respir Crit Care Med. A*, *55*.

Watson, M. A., King, C. S., Holley, A. B., Greenburg, D. L., & Mikita, J. A. (2009). Clinical and lung-function variables associated with vocal cord dysfunction. *Respiratory Care*, *54*(4), 467–473.

Weigand, L. A., & Undem, B. J. (2012). Allergen-induced neuromodulation in the respiratory tract. Retrieved from http://www.karger.com/Article/Abstract/336508

Weinberg, R. S., & Gould, D. (2011). Competition and Cooperation. *Foundations in Sport and Exercise Psychology*, 103–24.

Weinberg, R.S. & Gould, D. (2014). *Foundations of Sport and Exercise Psychology, 6E*. Human Kinetics.

Weinberger, M., & Doshi, D. (2017). Vocal cord dysfunction: a functional cause of respiratory distress. *Breathe*, *13*(1), 15–21. https://doi.org/10.1183/20734735.019316

Weiner, P., Azgad, Y., & Weiner, M. (1993). The Effect of Corticosteroids on Inspiratory Muscle Performance in Humans. *Chest*, *104*(6), 1788–1791. https://doi.org/10.1378/chest.104.6.1788

West, J. B. (2012). *Respiratory physiology: the essentials*. Lippincott Williams & Wilkins. Retrieved from https://books.google.com/books?hl=en&lr=&id=eLRjk-VDF3cC&oi=fnd&pg=PP2&dq=respiratory+physiology+the+essential+west+&ots=RmRO8AKvwV&sig=DJSujElxH14aM0NjePsAXhCIXLk

Widdicombe, J. G. (1998). Afferent receptors in the airways and cough. *Respiration Physiology*, *114*(1), 5–15.

Wiese-Bjornstal, D. M. (2010). Psychology and socioculture affect injry risk, response, and recovery in high-intensity athletes: a consensus statement. *Scand J Med Sci Sports*, *20*(Suppl. 2), 103–111.

Wilson-Pauwels, L., Akesson, E. J., & Stewart, P. A. (2002). *Cranial Nerves in Health and Disease*. PMPH-USA.

Witt, J. D., Guenette, J. A., Rupert, J. L., McKenzie, D. C., & Sheel, A. W. (2007). Inspiratory muscle training attenuates the human respiratory muscle metaboreflex. *The Journal of Physiology*, *584*(3), 1019–1028. https://doi.org/10.1113/jphysiol.2007.140855.

Wood II, R. P., & Milgrom, H. (1996). Vocal cord dysfunction. *Journal of Allergy and Clinical Immunology*, *98*(3), 481–485.

Yelken, K., Yilmaz, A., Guven, M., Eyibilen, A., & Aladag, I. (2009). Paradoxical vocal fold motion dysfunction in asthma patients. *Respirology (Carlton, Vic.)*, *14*(5), 729–733. https://doi.org/10.1111/j.1440-1843.2009.01568.x.

Yellowlees, P. M., & Kalucy, R. S. (1990). Psychobiological aspects of asthma and the consequent research implications. *CHEST Journal*, *97*(3), 628–634.

Younes, M., & Burks, J. (1985). Breathing pattern during and after exercise of different intensities. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *59*(3), 898–908.

Zając, A., Chalimoniuk, M., Maszczyk, A., Gołaś, A., & Lngfort, J. (2015). Central and Peripheral Fatigue During Resistance Exercise – A Critical Review. *Journal of Human Kinetics*, *49*, 159–169. https://doi.org/10.1515/hukin-2015-0118.

Zemlin, W. R. (1998). *Speech and Hearing Science: Anatomy and Physiology*. Allyn and Bacon.

Zhang, Z., Lai, H. J., Roberg, K. A., Gangnon, R. E., Evans, M. D., Anderson, E. L., … Lemanske, R. F. (2010). Early childhood weight status in relation to asthma development in high-risk children. *The Journal of Allergy and Clinical Immunology*, *126*(6), 1157–1162. https://doi.org/10.1016/j.jaci.2010.09.011