Perceptual Clinical Features in Exercise-Induced Laryngeal Obstruction (EILO): Toward Improved Diagnostic Approaches

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Abstract: Introduction. Athletes with exercise-induced laryngeal obstruction (EILO) (previously commonly referred to as paradoxical vocal fold motion disorder, or paradoxical vocal fold motion, among other terms) are often misdiagnosed, resulting in prolonged, and at times inappropriate, clinical management. The high prevalence of misdiagnosis is largely due to a lack of universal consensus of key clinical features indicating EILO and a dearth of validated quantitative approaches to accurately detect episodic laryngeal breathing disorders (ELBD) from other pathologies. Additionally, mechanisms underlying EILO clinical presentation are poorly understood, further confounding identification and management of the condition. Therefore, the objectives of this study were twofold. The first was to identify patient-centered perception of symptoms that could distinguish adolescent athletes with EILO from athletes without the condition, at baseline (rest) and during an exercise challenge (provocation), and to quantify symptom severities for use as preliminary diagnostic benchmarks. The second objective was to investigate the merit of one commonly proposed mechanism in the EILO literature—stress reactivity (temperament)—by comparing personality traits in athletes with and without EILO.

Methods. Twelve (12) athletes diagnosed with EILO and 14 healthy athletic volunteers without the condition were asked to rate the severity of their present symptoms using a 0−100 continuous visual analog scale. Participants then underwent an exercise challenge with simultaneous laryngoscopy and were asked to complete the same set of symptom severity ratings experienced during rigorous exercise. Finally, participants completed the Fear subscale on the early adolescent temperament questionnaire—revised (EATQ-R) to measure self-perceived levels of stress reactivity.

Results. There were significant group differences for inspiratory and expiratory dyspnea with exercise (P = 0.01). Symptoms of stridor (EILO: $P = .01$; control: $P = .001$) and throat tightness (EILO: $P = .01$, control: $P = .01$) were statistically different between rest and exercise in both groups. However, no group differences were found on these two parameters ($P > .05$). Other symptoms from the list of previously purported symptoms indicative of ELBD (e.g. cough, dysphonia) were infrequently reported in the exercise variant. Additionally, measurements of stress reactivity on the EATQ-R Fear subscale were similar between the two athletic groups. Interestingly, EATQ-R Fear Subscale scores for both groups were significantly higher compared to typical adolescents in the U.S. population ($P < .001$, respectively).

Discussion. Results suggest dyspnea severity, particularly when experienced during an exercise-induced ELBD (EILO) episode, is the most sensitive symptom parameter to distinguish individuals with EILO from those without the condition. These findings confirm previous literature describing episodic laryngeal breathing disorders in clinical cohorts. Results also showed symptoms of throat tightness and stridor is more prevalent during exercise, compared to rest. However, the level of their severity occurred variably across both groups of athletes and may point to a less robust indication of pathology. Finally, similarities to stress reactivity between the two athletic groups imply certain temperaments historically attributed to patients with EILO may instead better reflect temperaments in competitive young athletes, in general.

Conclusion. Study findings highlight the importance of using normative comparisons in the study of episodic laryngeal breathing disorders to prevent overgeneralization of characteristics to clinical cohorts. Results also speak of the clinical utility of exercise challenge to improve specificity of EILO diagnosis.

Key Words: Paradoxical vocal fold motion disorder−Exercise-induced laryngeal obstruction−Dyspnea−Shortness of breath−Temperament.

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INTRODUCTION

Clear diagnostic indicators of episodic laryngeal breathing disorders (ELBD)—which include the terms paradoxical vocal fold motion disorder and exercise-induced laryngeal obstruction (EILO) within the spectrum of upper airway breathing conditions—lack. Although there is no agreed-upon single etiology of ELBD, the most commonly cited symptom in the clinical literature is shortness of breath (dyspnea), attributed to airflow obstruction or restriction at the level of the larynx.[1] Although inspiratory dyspnea is typically cited as the "hallmark" characteristic of ELBD, literature also has reported patient complaints of dyspnea on expiration.[2,3] Additionally, various other symptoms, including hoarseness, cough, throat clearing, dysphagia, and globus sensation—to name a few—have been attributed to ELBD (see literature review by Shembel et al, 2017 for details).[4−7] Interestingly, not all symptoms from this extensive list appear in all clinical cases and reported patterns vary. There may be several reasons for this. The first may be that medical practitioners typically interact with symptom complaints specific to their specialty; the second may be that patient groups will vary according to the context in which they present with different symptoms to the clinic. For example, otolaryngologists will treat patients with dysphonia and therefore will be more inclined to include clinical characteristic surrounding voice complaints in patients with ELBD. In contrast, symptoms associated with swallowing (e.g., globus sensation, dysphagia) will be more representative of patient complaints seen in the gastroenterologist's office. Because interpretations of clinical features indicative of ELBD are siloed to medical domain, no universal consensus of symptoms representing ELBD exist. Furthermore, whether any of these symptoms are clinical *indicators* of ELBD or whether they reflect pathologies that commonly co-occur with or mimic conditions within the spectrum (e.g., muscle tension dysphonia and asthma, respectively), remains unclear. Finally, symptom benchmarks that could indicate severity of pathology lack due to gaps in study designs involving normal comparative cohorts. For example, shortness of breath, thought to be the hallmark symptom in ELBD, occurs with rigorous exercise, regardless of level of physical fitness. At one point does the sensation of feeling winded or out of breath become "abnormal" in individuals with ELBD?

With the lack of experimental evidence and dearth of standardized methods to identify and quantify ELBD presentation, clinical features indicating pathology are left open to interpretation. Inherent clinical biases can ensue, resulting in inaccurate diagnostic approaches. The lack of diagnostic clarity has also resulted in differential diagnoses based on exclusion as the current gold standard, which places heavy financial and resource burdens on the patient and medical system.[8,9] Finally, without standardized approaches, multidisciplinary communication becomes a challenge.

These concerns are nontrivial. Gaps in accurate diagnosis of ELBD likely contribute to the high prevalence of misdiagnosis (up to 90% rate) in the ELBD population[8−16] and can result in mismanagement for prolonged periods (average 7.5 years).[8,10,17] For athletes with an exercise-induced variant of episodic laryngeal breathing disorders (herein referred to as exercise-induced laryngeal obstruction, or EILO; refer to Røksund et al.[18] for details)—the focus of the present study—unnecessary inhaled corticosteroids and oral steroids, commonly administered to this population, can result in iatrogenic consequences such as osteoporosis, obesity, stunted growth, Cushing's disease, and hypertension in otherwise healthy, young individuals.[10,19−22] Protracted mismanagement can also mean missed collegiate scholarship opportunities and withdrawal from sports and the sports community, leading to feelings of isolation and impairment to self-concept.[23−26] Finally, from an academic perspective, unclear diagnostic definitions makes it challenging to identify appropriate cohorts for studies. Various interpretations of presentations that reflect pathology in patients with ELBD will likely result in different study outcomes.

To start addressing these substantial gaps, the overarching objective of this study was to begin to better define ELBD symptomology through a preliminary prospective study using an experimental and control cohort. The first study aim was to confirm robustness of dyspnea severity—the most prevalent symptom reported in the ELBD literature across medical domains—as a clinical indicator of pathology and to identify preliminary benchmarks of this parameter for future studies. The second goal was to identify the frequency of other symptoms commonly attributed to ELBD in the literature—chest tightness, cough, dysphagia, globus sensation, lightheadedness/dizziness, limb paresthesia, stridor (noisy breathing), syncope, systemic fatigue, throat clearing, throat tightness/constriction, and voice complaints (dysphonia/hoarseness)[27]—in one variant of EILO (exercise-induced) to better define the role of these parameters in ELBD pathology. Findings in this preliminary study serve as a springboard for future investigations within the EILO variant, as well as across various other clinical presentations of episodic laryngeal breathing disorders (e.g., irritable larynx syndrome, inducible laryngeal obstruction [ILO][28−31]).

In addition to gaps in identifiable features indicative of ELBD (in general) and EILO (more specifically), there are also gaps in our understanding of etiological mechanisms underlying these clinical presentations. Previous literature has frequently alluded to high stress reactivity and poor temperament/self-regulation as a cause of EILO[32−38]; these traits have been most commonly attributed to the high-achieving, competitive, and anxious nature in athletes with the exercise variant.[36,39] Unfortunately, this theory is largely unsubstantiated due to lack of empirical evidence. In fact, it could just as easily be that any athlete with a competitive drive and proclivity toward perfectionism could present with these traits [26,40,41] and may not necessarily be *indicative* of EILO. Furthermore, if there is a relationship between EILO and temperament (stress reactivity), determining whether the relationship is causal, consequential, or correlational is a worthwhile pursuit to improve management of the condition. Therefore, the third (exploratory) goal of this study was to compare stress reactivity in competitive young athletes, with and without EILO, using the *Fear* subscale of the early adolescent temperament questionnaire—revised (EATQ-R),[42] to determine whether temperament and emotionality do, in fact, play a role in EILO.

These preliminary findings should serve as platform for future investigations into potential mechanisms underlying ELBD clinical expression.

MATERIALS AND METHODS

Participants

Twenty-seven adolescent athletes (n = 13 EILO; n = 14 controls) were recruited for the study. Participants in both groups were eligible for the study if they were between the ages of 12−18 years and were involved in competitive extramural sports at least three times a week for a minimum of 40 minutes per session (refer to Table 2 in Results for complete list of sports/athletic activities). Participants enrolled in the experimental group were individuals with suspected EILO who presented with laryngeal-related symptoms (e.g., dyspnea, throat tightness) attributed to detriments to their athletic performance during practice or competition (it is important to note only data from participants with *confirmed* EILO, determined on physical examination, were statistically analyzed; details to follow). These individuals were recruited at the time of their initial consultation visit with the Speech-Language Pathology team at the Massachusetts Eye and Ear (MEE) Voice and Speech Laboratory. Patient referrals came from a comprehensive list of medical specialties in Boston and surrounding regions in Massachusetts. Specialists were all previously notified of the study via email blasts and advertisements as means to target a wide spectrum of patients with suspected EILO and to prevent siloed recruitment from the same medical domains (e.g., pulmonology, ENT, gastroenterology, pediatrics, cardiology, exercise medicine). All participants enrolled in the EILO group had previously undergone medical workups to exclude other pathology that could account for their dyspneic-related symptoms (e.g., asthma, allergies). Since the primary (hallmark) symptom of EILO reported across different medical domains is dyspnea (see review by Shembel et al, 2017 for details), the Dyspnea Index[43] (DI) was used to confirm appropriate individuals were being targeted for enrollment into the experimental group. The DI is a symptom-severity questionnaire which was previously validated in individuals with upper airway breathing pathology (see Gartner-Schmidt et al, 2014 for details). To be eligible for the study, all participants in the experimental group had to score at least a 10 out of 40 on the DI, which has previously been shown to be the benchmark to indicate upper airway breathing pathology.[43] All participants reported oxygen saturation levels to be normal (>95% SPO2) (confirmed during exercise provocation laryngoscopy). Participants with suspected EILO also were eligible for the study if they had no history of asthma (defined as FEV1 > 80% predicted) or if their asthma was well-managed (defined as FEV1 > 80% predicted with inhaler during methacholine challenge). The decision to include participants with well-controlled exercise-induced asthma into the experimental group was driven by the high prevalence of co-occurring asthma in the EILO population, previously documented in the clinical literature (30%−40% comorbidity).[44−46] First, we did not want to exclude individuals with EILO and asthma, especially since the goal was to cast a wide net of EILO presentations to more fully understand the breadth of the condition. Second, since bronchodilators (inhalers) temporarily open the airways, any symptoms related to dyspnea with FEV1 > 80% will be reflective of EILO and not exercise-induced asthma.[47−53]

The following combination of procedures increased confidence of accurate diagnosis and inclusion of participants with EILO: (1) extensive previous medical workup excluding other pathology as the cause of detriment to athletic performance, (2) the use of a symptom severity questionnaire previously validated in individuals with ELBD (Dyspnea Index), and (3) positive confirmation of laryngeal responsive patterns thought to be counterproductive to meeting metabolic demands (e.g., paradoxical vocal fold motion), identified on laryngoscopy once participants were enrolled in the study (details to follow). Additional methods and symptoms previously attributed to improving specificity of EILO diagnosis (albeit inconsistently, as shown in prior literature)[54] were also collected to gather a more comprehensive narrative of individuals suspected of EILO (see *Demographics* in Results section for details). These methods included the following: (1) where within the respiratory cycle the dyspnea occurred, (2) loci of tightness/constriction, (3) self-reported response to inhaled corticosteroids, (4) self-reported blood oxygenation levels during exertion (SPO2), (5−6) onset and offset of symptoms, and (7) additional open-ended questions regarding other associated symptoms with acute EILO episodes (see Appendix A for details). However, due to previously reported inconsistencies or lack of previous empirical validation of these methods to diagnose ELBD, these parameters were not *directly* used as inclusion criteria in the present study. Some of the parameters were reported descriptively (see *Demographics* section for details) while others were treated as potential auxiliary symptoms of EILO and included as dependent variables (details to follow). Other auxiliary methods, such as inspiratory flow volume loops and methacholine challenge, were not used in the study design due to their low sensitivity in diagnosing ELBD, shown in prior literature.[1]

Participants in the control group were recruited from local schools and sports teams in the New England region. Athletic volunteers were eligible for the control group if they had not previously experienced laryngeal-related symptoms 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 from the control group if they had a history of obstructive pulmonary disease or other medical conditions that could mimic symptoms attributed to ELBD (e.g., dysphonia, cough). Exclusion criteria for both groups were: (1) developmental, behavioral,

[1]E.g., See review by Morris et al., 2006 and Olivier et al., 2013 showing only 28%−29% of patients with ELBD exhibited inspiratory truncation of flow-volume loops when symptomatic and inconsistency of responses to methacholine challenge in a study by Perkins and Morris, 2002.[14,55,56]

or cognitive disorders that would make following directions during the study protocol difficult, (2) neuromuscular disorders that could affect exercise response, (3) cardiovascular conditions that would make the exercise challenge unsafe, (4) intolerance to flexible nasoendoscopy, or (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 athletic shoes that would allow them freedom of movement for exercise. Participants with well-managed asthma in the EILO group were also asked to bring their inhaler with them to the appointment.

Procedures

The study was approved by the Institutional Review board (Human Research Protections Program) at MEE. Once written informed consent was obtained, participants were asked to rate the severity of their symptoms from a list of common symptoms purported to be indicators of ELBD from previous literature. The list was based on a previous comprehensive literature review across 25 medical domains[27] (see Table 1 for complete list of symptoms). To be included in the checklist, symptoms had to be described in at least two articles written by different authors in differing medical domains. Participants were instructed to rate the severity of symptoms they were experiencing at the *present* moment using a 0−100 continuous visual analog scale (VAS). The benefit of the VAS, compared to symptom-specific quality of life questionnaires, previously validated in the ELBD population (e.g., Dyspnea Index,[43] vocal cord dysfunction questionnaire[57]), is that the VAS can assess symptom severities *during* acute ELBD episodes; the VAS has also been shown to have a strong linear relationship between symptom severity and exercise intensity.[58−62]

TABLE 1.
List of common ELBD-related symptoms, based on a comprehensive literature review. Refer to Shembel et al, 2017 for details

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)

Severity ratings were made three separate times within the study protocol. The first two times were at rest: before laryngoscopy (baseline) and during laryngoscopy without exertion (baseline laryngoscopy). The third time was at maximum exertion (laryngoscopy with exercise challenge). In addition to rating the severity of their symptoms, participants were also asked to rate the severity of their leg fatigue across the same three time points. The leg fatigue parameter was used both as a positive control foil and to confirm comparable fitness levels between the two groups. The list of symptoms and positive control foil were randomly presented to participants to minimize order effect.

The randomized symptom list was presented on a Fire HD-10 touch-screen tablet (Amazon Ltd.) using a customized VAS, created at www.surveygizmo.com. Each symptom had a corresponding 0−100 continuous horizontal line beneath it. Participants were asked to place a tick mark with their finger for each line on the tablet to represent the level of severity for each parameter. After each participant completed baseline severity ratings, participants completed the fear subscale of the EATQ-R[42] using the same digital touch-screen tablet. The EATQ-R, overall, measures different temperament constructs. The fear subscale on the EATQ-R, specifically, measures levels of perceived unpleasantness and negative affect associated with anticipation of stressful events (i.e., stress reactivity).[42] This subscale is thought to correlate with high levels of anxiety and neuroticism in adolescents.[63,64]

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 placed on the participant's chest and right arm, respectively, to monitor vitals and ensure safety of the participants. Oxymetazoline (nasal decongestant) was then administered into the nostrils in accordance with standard of care procedures at MEE 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 (i.e., 8 on the scale). Patients with suspected EILO were instructed to give a “thumbs up” sign when they experienced symptoms representative of complaints typical during their respective sport (s) or other competitive athletic activities. Once participants indicated understanding, the seat of the stationary bike (SF-B1203 Indoor Cycle Trainer) was adjusted to each participant's configuration. Target ergonomics were a slight bend at the knee joint (10°−15° angle) and comfortable extension of the arms on the handlebars for stability.[65,66]

Participants sat on the trainer 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 oropharynx into the laryngeal vestibule. Once the endoscope 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 (of note, no participants met his exclusionary criteria). Participants again rated symptoms on the VAS during the baseline laryngoscopy for later comparisons and to preemptively account for potential differences in symptom reporting with introduction of the endoscope (of note, no differences were found between the two baseline conditions, and therefore prelaryngoscopy baseline ratings were used for the rest condition in the statistical analysis). Video recordings of the larynx (*n*Stream G3, Image Stream Medical) were then initiated with the exercise challenge. 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 images were captured and recorded to confirm no paradoxical movement was seen on the laryngoscopy video and to parallel the protocol with the EILO group. The exercise protocol was then terminated and the endoscope was removed. For participants with suspected EILO, resistance increased incrementally every 30 seconds until an EILO episode was induced. Thirty (30) seconds of the provoked episode were video recorded before participants in the EILO group were asked to cease pedaling. The physical examination was considered positive for EILO (and subsequent clinical diagnosis of ELBD was provided) if there was concurrence of (1) patient-perceived symptoms representative of symptoms experienced during regular athletic activity (indicated with “thumbs up” signal) and (2) lateral−medial or anterior−posterior laryngeal movement patterns (e.g., paradoxical adduction of the vocal folds; prolapse or quivering of the arytenoids) or any other types of constriction or obstruction patterns that could hinder the respiratory system's ability to meet the body's metabolic needs. 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 EILO group were asked to rate the severity of their episode, compared to symptoms typically experienced with their respective sports/athletic activities.

Symptom severity scores (1−100 VAS) acquired during rest conditions (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. Prevalence of symptoms reported in the EILO group from the list was descriptively identified to determine which symptoms were most common in the experimental group; the most prevalent symptoms were then statistically analyzed between groups and conditions. Severity of leg fatigue also was statistically analyzed to assess consistency between groups and ensure that groups reached equivalent exertion levels. Of note, data violated assumptions of normality and variance, requiring nonparametric statistical analysis. Therefore, Kruskal Wallis H tests were conducted to determine group differences (EILO, control) while Wilcoxon Signed-Ranks tests were conducted to determine whether there were significant condition differences across the two groups (rest, exercise). All nonparameteric statistical analyses were corrected for Type 1 error with Bonferroni corrections. Independent samples t tests also were conducted for responses on the EATQ-R fear subscale to determine group differences.

RESULTS

Demographics

The mean age of participants was 14.46 years (SD = 1.94) for the EILO group and 16.87 (SD = 1.19) for the control group. There were 9 females and 4 total males enrolled in the EILO group, and 9 females and 5 males enrolled in the control group. Positive provocation, defined by patient-reported symptoms and concurrent laryngeal pattern changes, was not evoked in 1 of the 13 participants in the EILO group; therefore, data for that participant were subsequently removed from statistical analysis. The 2:1 prevalence in female-to-male ratio in the EILO group is consistent with previous literature showing EILO affects twice as many females as males (as compared to the 3−5 times greater female prevalence in other types of ELBD, e.g., irritant-induced).[67] Participants in the EILO 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 EILO 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 EILO 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 EILO 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 second) in the EILO group and 265.71 seconds (SD = 48.48 second) in the control group. See Table 2 for a summary of participant demographics and average level of athleticism for each group.

The average reported length of time to onset of EILO episodes experienced in the experimental group during typical sports-related activities (outside of the clinical setting) was 5.78 minutes (range 30 seconds−15 minutes) and average reported complete resolution of symptoms was 16.38 minutes (range 2 minutes−2 hours). All 12 participants diagnosed with EILO had been prescribed a trial course of inhalers by a general practitioner or pulmonologist prior to

TABLE 2.
Demographics of EILO and Control Groups. Group Comparisons Show Both Groups of Athletes Were Similar in Age and Gender. Both Groups Participated in Aerobic-Type Athletic Activities ~5 Times a Week for 1.5–2 h. Both Groups Also Exerted Themselves Similarly With the Exercise Challenge and the Amount of Time it Took to Achieve Maximum Exertion on the Stationary Bicycle Between the Two Groups was Comparable

Group	Age	Gender	Aerobics/Sports*	Times/Week	Session Length (min)	Effort Level (1–10)	Dyspnea Index	Time to Max Exertion (s)
EILO	14.46 ± 1.94	9 F 3 M	1 Basketball 1 Crew 3 Cross country/ Track and 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 and 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

* Several participants played multiple sports.

their initial consultation at MEE Voice and Speech Laboratory. The average improvement in self-perceived symptoms with inhalers was 29.58% (range 0%–85%). Of the 12 participants, 9 of the participants reported less than 50% improvement with inhalers.

The prevalence of concomitant asthma in the EILO group was 33% (confirmed with pulmonary function testing), which is consistent with previous literature suggesting asthma co-occurs in 30%–40% of patients with EILO.[44–46] Diagnosed environmental allergies were also prevalent in 33% of patients with EILO in the present study; confirmed gastroesophageal reflux disease in 17% of the EILO participants. Clinically diagnosed generalized anxiety disorder was found in 8% of the EILO participants. Three out of 12 participants (25%) in the EILO group reported extreme temperatures and environment (e.g., heat, cold, dry air, humidity) amplified symptoms experienced with exertional activity (in contrast, no medical history of allergies, asthma, or psychological conditions were found in the control group). Mean severity of EILO symptoms experienced with the protocol's exercise challenge (compared to typical sports-induced episodes, previously noted) was 7.30 (range: 5–9; scale: 1 = no symptoms, 10 = most severe episode experienced). Eleven out of 12 participants reported inspiration was typically more challenging than expiration during physical activity (e.g., soccer games), although all participants in the EILO group experienced some levels of shortness of breath during both inspiratory and expiratory cycles. The 12th participant reported expiration and inspiration were equally challenging.

The four bolded symptoms in Table 3—inspiratory dyspnea, expiratory dyspnea, stridor, and throat tightness—indicate the most prevalent features (≥50%) reported in the EILO cohort. The other (nonbolded) symptoms in Table 3—chest tightness, cough, dysphagia, globus pharyngeus, dizziness, paresthesia of the limbs, systemic fatigue, throat clearing, and voice complaints—were less prevalent in the EILO cohort (<50%). Therefore, severities of these latter features were not statistically analyzed.

Symptom severity ratings

Inspiratory dyspnea

On average, participants in the EILO group reported greater inspiratory dyspnea than the control group in both baseline and exercise conditions (Figure 1). These group differences were statistically significant with exercise ($P = .01$) but not at baseline ($P = .09$). As can be expected with heavy

TABLE 3.
Common symptoms and Prevalence of Symptoms in EILO group. The Following is the List of Symptoms Associated With ELBD, Based on a Literature Review by Shembel et al, 2017 (Left Column) and Prevalence of Symptoms Reported in EILO Group of the Present Study (Right Column). The Four Bolded **Symptoms: Inspiratory Dyspnea, Expiratory Dyspnea, Stridor, and Throat Tightness Indicate the Most Prevalent Features Reported in the EILO Cohort (50% or greater)**

Perceptual Symptom Parameters	# (%) of 12 EILO Participants
Chest tightness	3 (25%)
Cough	1 (8%)
Dysphagia (swallowing complaints)	1 (8%)
Globus sensation	1 (8%)
Lightheadedness/dizziness	2 (17%)
Limb paresthesia	1 (8%)
Shortness of breath with expiration	**8 (67%)**
Shortness of breath with inspiration	**12 (100%)**
Stridor (noisy breathing)	**6 (50%)**
Syncope	0 (0%)
Systemic fatigue	1 (8%)
Throat clearing	2 (17%)
Throat tightness/constriction	**6 (50%)**
Voice complaints (dysphonia/ hoarseness)	2 (17%)

exertion, both groups reported significantly higher inspiratory dyspnea severity ratings during the apex of the exercise challenge, compared to baseline (EILO: P = .002; control: P = .001).

Expiratory dyspnea

As with inspiratory dyspnea, average severity ratings of expiratory dyspnea were higher in the EILO group compared to the control group, both at rest and with exercise (Figure 2). Statistical analysis showed these group differences were statistically significant both at rest (P = .02) and with exercise (P = .01). Statistical analysis for condition showed participants in both groups rated significantly higher expiratory dyspnea with exercise, compared to rest, as well (P = .003, respectively).

Stridor

Average severity levels of self-reported stridor (noisy breathing during inspiration), both at baseline and with exercise, were similar between groups (Figure 3) and statistical analysis confirmed there were no significant group differences ($P > .05$, respectively). However, there were significant condition differences seen in both the EILO (P = .01) and control groups (P = .001) from rest to rigorous exercise.

Throat tightness

On average, participants in the EILO group reported more throat tightness than the control group, both at baseline and exercise (Figure 4). However, group differences were not statistically significant at either baseline or exercise conditions ($P > .05$). Statistically significant condition differences between baseline and exercise conditions were seen in both the EILO and control groups (P = .01, respectively).

Leg fatigue

Results on leg fatigue ratings showed the two groups perceived comparable levels of exertion at both baseline and exercise (Figure 5). Statistical analysis confirmed these findings by demonstrating there were no group differences at either rest or exercise ($P > .05$). As can be expected, both groups reported significantly higher levels of leg fatigue with rigorous exercise, compared to rest (EILO: P = .002; control: P = .001).

Temperament and stress reactivity (EATQ-R fear subscale)

There was one outlier in the data within the EILO group, as assessed by boxplot. EATQ-R Fear subscale responses were

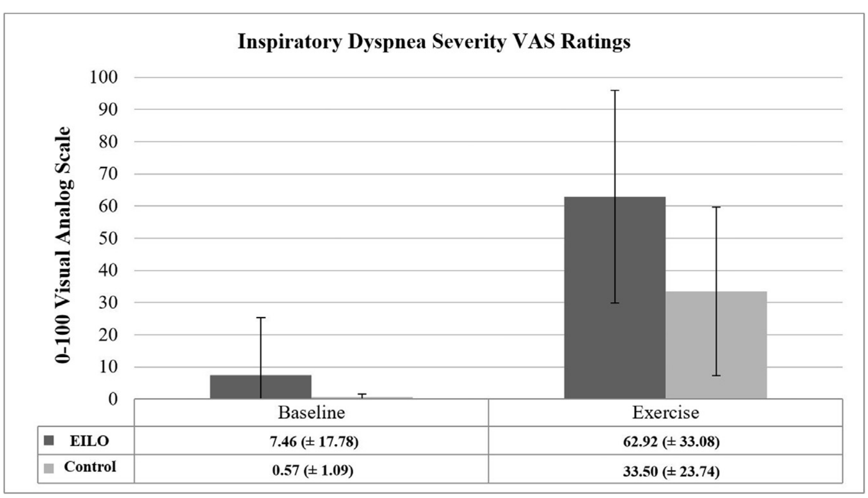

FIGURE 1. Inspiratory dyspnea severity scores at rest and exercise. Results showed group and condition differences.

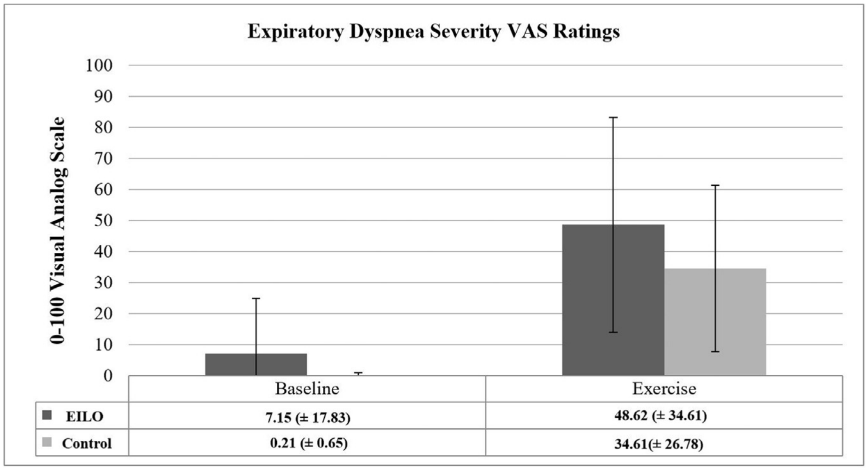

FIGURE 2. Expiratory dyspnea severity scores at rest and exercise. Results showed group and condition differences.

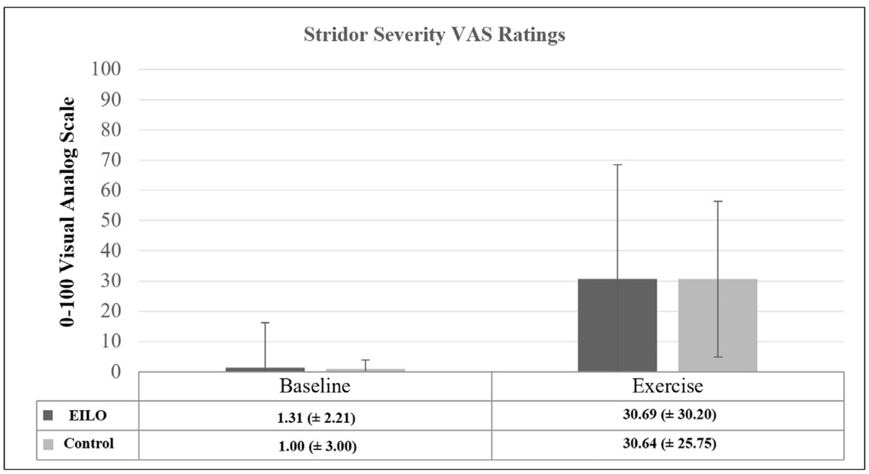

FIGURE 3. Stridor severity scores at rest and exercise. Descriptive and statistical differences between conditions were found; no differences were seen between groups at baseline or exercise.

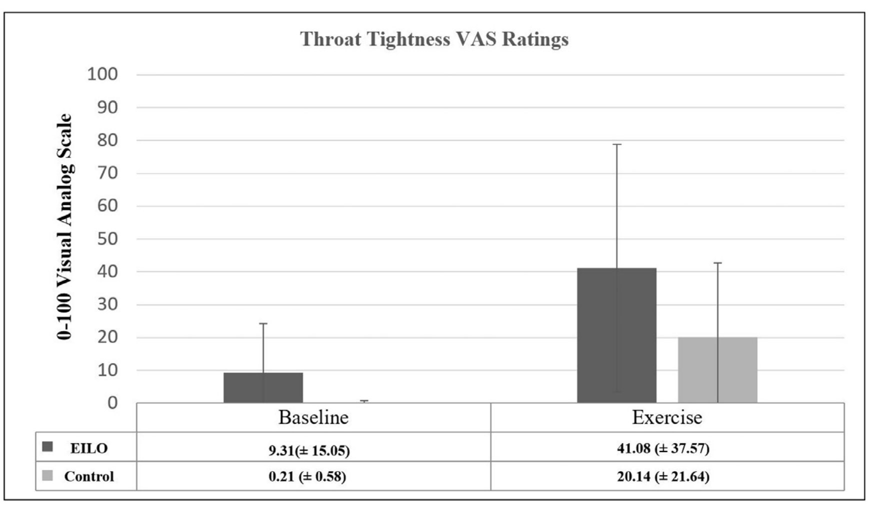

FIGURE 4. Throat tightness severity scores at rest and exercise. Significant condition differences were seen from rest to exercise in both groups; however, no group differences were found. The lack of significant group findings, despite descriptive group differences across conditions, is attributed to high variability (see standard deviations) in perceptions of severity for the throat tightness parameter.

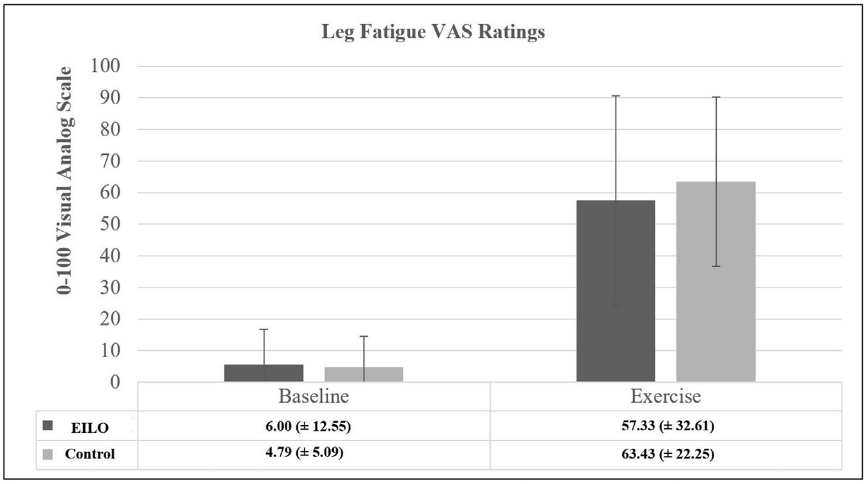

FIGURE 5. Leg fatigue severity scores at rest and exercise. Results showed groups experienced similar levels of exertion.

normally distributed, as assessed by Shapiro-Wilk's test ($P > 0.05$) 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 EILO 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[63]—did show statistically significant differences amongst the EILO, athletic control, and general population cohorts, respectively ($P < 0.001$) (Figure 6).

A summary of the findings can be found in Table 4. Comparisons with this current study and previous literature have also been included in the table.

DISCUSSION

Findings from this prospective study generally corroborate with clinical descriptions of ELBD in the academic literature. From the comprehensive list of symptoms thought to indicate ELBD, dyspnea (inspiratory and expiratory) appeared to best correlate with the exertion-induced ELBD variant. Although participants in the present study reported both inspiratory and expiratory dyspnea with exertion, the dyspnea ratings with inspiration were, on average, more severe than with expiration. Results also showed that symptoms of stridor (noisy breathing on inhalation) and throat tightness may accompany primary symptoms of dyspnea in patients with EILO.

More specifically, all patients in the EILO group reported they experienced dyspnea severe enough to cause detriments to athletic performance. Quantitatively, there were significant differences between baseline and exertion on dyspnea severity scores in response to exercise challenge between participants with and without EILO. It is important to stress that the mere *presence* of dyspnea should not be used as a diagnostic indicator, since both groups experienced dyspnea with exercise. Stated differently, rigorous physical activity causes shortness of breath and feelings of breathlessness, regardless of aberrant laryngeal breathing patterns or athletic abilities. Benchmarks of severity ratings of dyspnea during acute episodic events, however, could be used as indicators of pathology within the framework of diagnostic approaches, thus helping improve diagnostic specificity. For example, an inspiratory dyspnea rating greater than 30/100[2] on the VAS with exercise challenge, as demonstrated by the dyspnea severity ratings in the present study, may help differentiate individuals with EILO from those without the condition. Clinical benchmarks not only improve accuracy of diagnosis but also can be used to appraise treatment outcomes and identify appropriate cohorts for future studies. That being said, additional validation of these severity benchmarks in larger cohorts and comparison studies across different clinical cohorts with similar symptoms (e.g., asthma, muscle tension dysphonia) are needed to further define dyspnea severity benchmarks for improved identification of pathology.

Symptom severities of stridor and throat tightness, also commonly reported in the EILO cohort, showed these symptoms occurred variably across individuals in both EILO and control groups (*c.f.,* Figure 3 and Figure 4). In other words, although participants in both groups rated stridor and throat tightness as more severe with exercise, compared to rest, there were no significant differences between the groups, likely due to high variability in responses. These preliminary findings suggest that although stridor and throat tightness can accompany symptoms of dyspnea in the EILO population, they may not necessarily be *indicative* of pathology. Results also suggest perceptions of stridor and throat tightness, found variably in both groups of athletes, but reported higher with rigorous exercise compared

[2]Based on the lower boundary of mean and standard deviation for inspiratory dyspnea severity ratings in the EILO group (M = 62.92 ± 34.48).

TABLE 4.
Summary of Study Findings and Comparisons between Current Study and Previous Work. (A) Expert Opinion Column is Based on Work by Christopher and Morris, 2010; Gallena et al, 2013; Hoyte, 2013; Nascimento et al, 2013; Ritz, Steptoe et al, 2006; Sarafino and Goldfedder, 1995; Tilles and Inglis, 2009;[15,16,44,46,68–70] (B) Patient Self-Reported Column is Based on a Prospective Study by Bernstein (2014);[8] (C) Self-Reported and empirical Evidence in Present Study. Similarities can be Found in the Following Parameters: Onset of Symptoms and Presence of Inspiratory Dyspnea. Discrepancies Can Be Found in the Timing of Noisy Breathing Within the Respiratory Cycle, Recurrence Rates of Symptoms, duration of Recovery Without Treatment, and Prevalence of Throat Tightness (Response to Bronchodilators May be More Variable, Possibly Due to Placebo Affect or Unknown Underlying Mechanisms). These Latter Findings Suggest These Presentation Parameters as a Diagnostic Differential Might Require Their Use With Caution

Parameter	(A) Expert Opinion	(B) Self-Reported (Previous Study; Bernstein 2014)	(C) Self-Reported and Empirically Analyzed (Present Study)
Onset of symptoms	ELBD: Immediate (within 5 min)	ELBD: 69% immediate (within 5 min)	EILO: *Ave.* = 5.78 min (range: 30 sec—15 min)
Resolution	ELBD: May take less than 10 minutes	ELBD: 65% symptoms lasted longer than an hour without treatment	EILO: *Ave* = 16.38 min (range: 2-180 min)
Tightness	ELBD: In throat	ELBD: 90% in throat 65% in chest	EILO: 50% in throat 25% in chest Group comparisons: No significant differences in severity of throat tightness between healthy and EILO athletes ($P > 0.05$).
Difficulty breathing	ELBD: On inspiration	ELBD: Not addressed	EILO: Inspiration > Expiration in 11/12 participants Inspiration = Expiration in 1/12 participants Group comparisons: Significant difference between healthy and EILO athletes for inspiratory dyspnea and expiration with exertion only ($P = .01$).
Noisy breathing	ELBD: Stridor present (inspiration)	ELBD: 50% stridor (inspiration) 40% wheeze (expiration)	EILO: 50% stridor (inspiration) 33% wheeze (expiration) Group comparisons: No significant differences in severity of stridor between healthy and EILO athletes for stridor ($P > .05$).
Recurrence	ELBD: Symptoms can occur immediately and more severely when trigger resumes	ELBD: 40% recurrence worse with re-initiation of trigger	EILO: 67% recurrence worse with re-initiation of exercise
Medications	ELBD: Bronchodilators won't help	ELBD: 6% resolution with bronchodilators	EILO: 29.58% (range 0%–85%) improvement with bronchodilators (<50% improvement in 9/12 participants)

ELBD, episodic laryngeal breathing disorders.

to rest, may have more to do with the physiological demands in athletes, in general, and less to do with an EILO diagnosis, specifically. Additionally, the features that were less commonly reported in the EILO group, from the list of potential symptoms attributed to ELBD in prior literature (*c.f.,* Table 3) may better reflect other ELBD trigger variants (e.g., irritant-induced), other types of ELBD (e.g., irritable larynx syndrome), or other concomitant pathologies (e.g., chronic cough, muscle tension dysphonia, asthma). However, further investigations are needed to understand the roles of these other symptoms in the context of laryngeal breathing disorders.

Of note, we recognize the somewhat circular logic to accurately identify individuals with EILO for this study. How can one be sure the appropriate individuals were recruited without robust diagnostic methods to guide inclusionary criteria? Although this work used an extensive literature review across 25 different medical domains to guide the experimental design, there is always the possibility of incorrect diagnosis. However, further work can use this *preliminary* study as a springboard to confirm or refute these findings. More systematic, evidence-based approaches to studying EILO (specifically) and ELBD (in general) are of utmost importance; we aimed to provide a small scaffold in the grand scheme of this line of work.

Finally, results on the EATQ-R Fear subscale suggest athletes with EILO may have analogous temperaments to other competitive athletes (*c.f.,* Figure 6). Future caution should be taken so as not to over-attribute emotionality and temperament to EILO. Future study is also needed to determine whether temperament plays a role in other types of ELBD and therefore it is ill-advised to generalize these findings to other cohorts within the ELBD spectrum until causal investigations can be made. Finally, it is important to recognize one limitation surrounding the EATQ-R: the measurement assesses the *perception* of anticipated stressful events in athletes but does 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.[71] Therefore, future investigations 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 EILO 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 EILO.[72]

Results from this study showing clinical symptom differences between groups could help guide future etiological investigations into mechanisms driving clinical expression of EILO. For example, increased levels of dyspnea and throat tightness reported in individuals with EILO, especially during *asymptomatic* nonprovoked periods with observed concurrence of normal laryngeal movement patterns, could point to a disrupted somatosensory system. Or, these unprovoked symptoms at baseline could be the result of musculoskeletal dysfunction outside of the intrinsic laryngeal musculature. It is important to remember that various other muscles of the head and neck (e.g., pharyngeal dilators, perihyoid muscles) are also involved in airway patency; therefore, upper airway musculature could be involved in respiratory modulation and may play a role in dyspneic sensations at rest. These sensations could then be further exacerbated with increased musculoskeletal effort typical of exertion. Just as leg muscles can become tight and stiff with repetitive use, such as with long-distance running, causing decrements to subsequent athletic performance, so can accessory muscles of the upper airways become tense with chronic or heavy exertion.

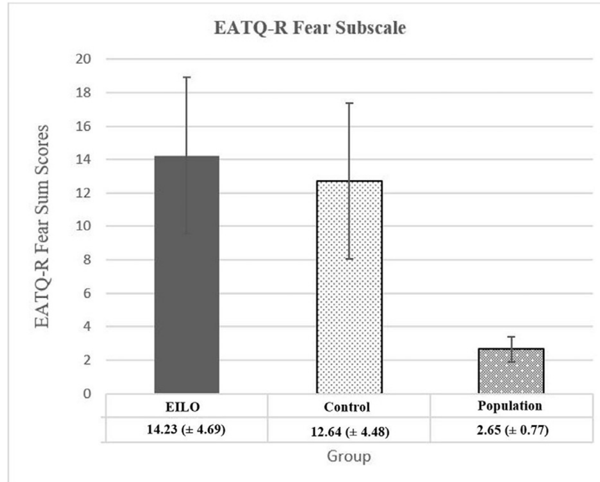

FIGURE 6. Comparisons between study group and general population EATQ-R fear subscale scores. Significant differences were found between the athletic groups and normative data for typical adolescents (Ellis et al., 1999).

CONCLUSION

This prospective study was the first step in a programmatic line of work to help improve diagnostic accuracy for ELBD. Results show inspiratory and expiratory dyspnea are good perceptual correlates in the exercise-induced variant. Preliminary severity benchmarks (e.g., >30 out of 100 on VAS) from the present study can be used to help identify pathology and determine the level of disability, thus reducing the prevalence of misdiagnosis and mismanagement in patients with EILO. Replication studies with larger cohorts and study designs with other disorders with overlapping symptomology to ELBD (e.g., asthma, COPD, panic disorders) are needed. These findings should be studied in relation to normal variation in exercise intolerance as a result of normal physiological limitations (e.g., deconditioning). In addition to studying normative benchmarks for pathology using perceptual features that correlate with ELBD, physiological studies are also needed to better elucidate etiology underlying symptoms. Outcomes of this study can aid future academic investigations into physiological and etiological factors causing ELBD, as well as guide clinical diagnostic approaches to the condition.

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APPENDIX A. EILO DIFFERENTIAL DIAGNOSIS QUESTIONS

- Is it harder to breathe:

In / Out / Both / Neither / Can't Remember

(circle one) 1

Please make "level in

Comment: ____

- Where does the air get stuck/do you feel tightness?

Throat only / Chest only / Both / Lower throat/Upper Chest / Neither

(circle one) P

Comment: ____

- Have you been given an inhaler? Yes / No (circle one)

If yes, does it help? Yes No Sometimes

Improvement Level: ___%

Do you still use it? Yes / No / Sometimes (circle one)

Comment: ____

- Have your blood oxygen levels ever been checked during an episode? Yes / No (circle one)

If yes, what was the reading during the episode? _______ __________%

- How long does it take to start?

____

- How long does it take to calm down?

____

- Any other symptoms you experience (cough, feeling like there is a lump in your throat, voice changes)?

NOTES:

____

____

Source: Courtesy of Catherine Ballif, M.A. CCC-SLP, Massachusetts Eye and Ear Infirmary, Boston MA. Adapted from Mathers-Schmidt 2001

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