Inducible laryngeal obstruction during exercise: moving beyond vocal cords with new insights

James Tod Olin1, Matthew S. Clary2, Emily H. Deardorff3, Kristina Johnston3, Michael J. Morris4, Mofiyinfolu Sokoya2, Herman Staudenmayer5 and Kent L. Christopher6

1Department of Pediatrics, National Jewish Health, Pediatric Exercise Tolerance Center, Denver, CO, USA, 2Department of Otolaryngology, University of Colorado, Aurora, CO, USA, 3National Jewish Health, Denver, CO, USA, 4San Antonio Military Medical Center, Internal Medicine, San Antonio, TX, USA, 5Private Practice, Denver, CO, USA, and 6School of Medicine, University of Colorado, Aurora, CO, USA

Abstract
Exercise as an important part of life for the health and wellness of children and adults. Inducible laryngeal obstruction (ILO) is a consensus term used to describe a group of disorders previously called vocal cord dysfunction, paradoxical vocal fold motion, and numerous other terms. Exercise–ILO can impair one’s ability to exercise, can be confused with asthma, leading to unnecessary prescription of asthma controller and rescue medication, and results in increased healthcare resource utilization including (rarely) emergency care. It is characterized by episodic shortness of breath and noisy breathing that generally occurs at high work rates. The present diagnostic gold standard for all types of ILO is laryngoscopic visualization of inappropriate glottic or supraglottic movement resulting in airway narrowing during a spontaneous event or provocation challenge. A number of different behavioral techniques, including speech therapy, biofeedback, and cognitive-behavioral psychotherapy, may be appropriate to treat individual patients. A consensus nomenclature, which will allow for better characterization of patients, coupled with new diagnostic techniques, may further define the epidemiology and etiology of ILO as well as enable objective evaluation of therapeutic modalities.

Keywords: Continuous laryngoscopy during exercise, exercise-induced laryngeal obstruction, exertional dyspnea, inducible laryngeal obstruction, paradoxical vocal fold motion, vocal cord dysfunction

Introduction
The first descriptions of the periodic occurrence of laryngeal obstruction associated with dyspnea and noisy breathing were recorded by Dunglison in 1842, followed by Austin Flint in 1868, and Osler in 1902 [1-3]. However, MacKenzie was the first to visualize abnormal vocal fold motion in 1869 [4]. In 1983, Christopher et al. published the first comprehensive description of the syndrome of vocal cord dysfunction (VCD) presenting as asthma [5]. Episodes of dyspnea and noisy breathing mimicked asthma, but asthma was excluded by bronchial challenge testing. Laryngoscopic examination confirmed that characteristic features of abnormal inspiratory vocal fold adduction occur only during symptomatic episodes. Patients were asymptomatic at the time of follow up after combined treatment with speech-language pathology and psychotherapy.

Since the 1980s, it has become clear that episodic laryngeal obstruction is much more common than previously recognized. It is important for its impact on quality of life (impairing the ability to meet exercise goals), medication use (as it is frequently misdiagnosed as asthma), and increased healthcare resource utilization [6]. Historically, it has been diagnosed via a combination of clinical history, pulmonary function testing, and laryngoscopic visualization. The 2012 review in The Physician and Sportsmedicine highlighted many of the diagnostic considerations for symptoms provoked by exercise [7].

Over the past few years, there have been developments which will advance our understanding of episodes of laryngeal obstruction, particularly in regard to impact on exercise. First, an international task force has created a nomenclature consensus which defines the group of disorders using ‘inducible laryngeal obstructions causing breathing problems’, abbreviated as ‘ILO’, with sub-categorization of disorders by specific triggers or inducers (e.g. exercise-ILO) [8]. This development may improve communication and enable studies across centers. Second, continuous laryngoscopy during exercise, a procedure during which the larynx is visualized for several minutes during an exercise challenge, is more commonly used nowadays [9]. This development will ideally improve the diagnostic capabilities of many centers. Finally, a newly proposed symptom metric, the Dyspnea Index, initially validated for use in patients with dyspnea caused by upper airway pathology of multiple etiologies, has been
published for use in young patients with exercise-ILO to quantitatively track symptom severity over time following a single-arm, non-placebo-controlled trial [10]. These approaches may lead to improved objective analysis of therapeutic interventions. The following is a state-of-the-art discussion of present knowledge regarding exercise-ILO taking these new directions into consideration.

**Methods**

This review was created by a subset of members involved in an upper airway working group, based in Denver, Colorado. The group comprising pulmonologists, otolaryngologists, clinical psychologists, psychiatrists, and speech-language pathologists focused on the ultimate development of clinical trials for ILO. Dr Kent L. Christopher and Dr Michael J. Morris have been leaders in this field for decades. The literature from these relevant specialties was reviewed and discussed over several weeks by the primary authors of this review, which was invited by the editorial staff of *The Physician and Sportsmedicine*.

**Definitions and new nomenclature**

Over 40 terms have been used to describe disorders characterized by symptomatic episodes of laryngeal obstruction (Table 1). The acronym VCD is used predominantly by pulmonologists, allergists, and respiratory therapists. In contrast, the term ‘paradoxical vocal fold motion’ has been used primarily by otolaryngologists and speech-language pathologists to describe endoscopic findings of periodic symptomatic adduction of the vocal cords. Similar symptoms of dyspnea and noisy breathing, particularly during exercise in adolescents and young adults, have been reported with supraglottic narrowing on laryngoscopy [11]. The term ‘laryngomalacia’ has been used to describe inspiratory supraglottic collapse during exercise, although histological features of laryngeal chondromalacia have not been confirmed. In some individuals, supraglottic prolapse during exercise may be preceded or accompanied by abnormal vocal fold adduction during breathing [12].

It is the authors’ collective opinion that the lack of an international standard on nomenclature inhibits organized research on these conditions for several reasons. At a fundamental level, two patients with similar findings may be characterized differently (or two patients with somewhat different findings may be characterized similarly) across treating clinicians and institutions. Consequently, it has not been possible to conduct well-organized studies designed to evaluate epidemiology, etiology, pathophysiology, diagnostic testing, and treatment of these laryngeal disorders.

To solve the problem related to terminology heterogeneity, an international task force of 13 multispecialty experts from 9 countries supported by the European Respiratory Society, European Laryngological Society, and American College of Chest Physicians was assembled. The task force reviewed the literature and reached a consensus on nomenclature. The consensus term for the group of conditions noted above was ‘inducible laryngeal obstruction causing breathing problems’, with an umbrella acronym of ‘ILO’ [8] The term was based on the sudden onset of symptoms with variable time courses of symptom resolution, the general location of airflow limitation, and symptoms characterized generically as ‘breathing problems’. The group excluded mimics of ILO from the group of conditions encompassed (e.g. tracheomalacia, tracheal stenosis, and asthma).

The group concluded that subcategories of patients with ILO should be defined by inducer(s) of attacks and laryngoscopic findings. Inducers are the associations the patient identifies with the event and are not intended to represent mechanisms or etiology of the episodes. The inducer subcategories most relevant to the athlete or casual exerciser include exercise and emotional stress. The laryngoscopic findings of critical importance include the description and timing of the glottic and/or supraglottic behavior (inspiratory, expiratory, or biphasic change from baseline to the point of maximal obstruction), as well as the conditions under which testing occurred (spontaneous attack versus controlled provocation.
testing, exercise intensity level, and timing of laryngeal change in respect to exercise).

The nomenclature and subcategories of ILO allow for international standardization of descriptions and categorization of these disorders. The authors believe that this foundation may promote international data sharing and enhance our understanding of the epidemiology, etiology, pathophysiology, appropriate diagnostic testing, and treatment of individual disorders.

Epidemiology and impact

Epidemiological statistics describing ILO are difficult to ascertain due to the heterogeneity in terminology (noted above), diagnostic techniques, and diagnostic criteria. In the only general population screened for exercise-ILO, a high proportion (>80%) had observed findings, although the correlation with symptoms was not reported [12]. In active duty members of the US military, exercise-ILO was found to be the underlying disorder in 15% of patient presenting with exertional dyspnea [13,14]. Whereas ILO of any cause has been reported to affect 3–5 times the number of females as males, exercise-ILO is reported to affect only twice as many females as males [15-17].

The overall impact of exercise-ILO is also difficult to estimate because it is challenging to clearly define events outside the pulmonary laboratory. Based on our collective clinical experience, there may be several domains of impact, each with varying importance in the life of a patient (Table 2).

Athletes present to clinicians because athletic performance is impaired by dyspnea. In certain sporting events, such as middle distance running and swimming, or with military personnel, it may be quite easy to estimate the performance decrement caused by dyspnea in terms of time. In other sporting events, especially in team sports, quantifying impairment is more challenging. Many athletes, especially those who perform short sprint events, note that the ability to train (rather than compete) is most affected by dyspnea, although other athletes report notable limitation only in competition. The emotional stress in competitive sporting events, especially in the presence of excessive expectations, may result in an emotional stress-ILO.

Professionals present to clinicians because dyspnea limits their ability to complete occupational tasks. Firefighters, police officers, and military personnel are generally expected to demonstrate competence in physical fitness testing. The consequences of testing failure can contribute to performance-related anxiety, thereby worsening symptoms. More importantly, severe dyspnea during dangerous situations can theoretically jeopardize the lives of patients and others.

The iatrogenic impact of ILO has been most readily quantified in the literature in the past in terms of unnecessary prescription of medications used in treating asthma and other respiratory disorders [15]. Oral corticosteroids and costly combination metered-dose inhalers are two of the most commonly implicated medications. High utilization of healthcare has been described [6]. There is often a high cost to diagnostic testing for this often difficult-to-diagnose condition. In clinical practice, patients with exercise-ILO are often not considered to have an upper airway disorder and laryngoscopy is not done early in the evaluation. This may lead to unnecessary evaluations for the presence of severe cardiac disease, fixed airway stenosis, seizures, brain stem abnormalities, esophageal disease, severe psychiatric disease, and malingering.

From a public health perspective, especially in an age when exercise is advocated to be as important in maintaining health as some medicines, it is possible that the largest impact of exercise-ILO is its ability to discourage recreational exercisers from participating in otherwise healthy activities. We may never know the frequency of this scenario nor how many quality adjusted life-years are lost, but this is a scenario which clinicians must consider.

Severe, life-threatening exacerbations of ILO that do not respond to exercise termination are considered rare (although seminal literature describes the use of tracheostomy in a few ILO patients where the inducer event was not specifically identified as exercise) [5]. However, exercise-ILO patients occasionally report syncope and presyncope. A potential mechanism is (somewhat counterintuitive) hyperventilation, leading to cerebral hypoperfusion and poor tissue oxygenation.

The authors feel that an important gap in present knowledge is our current inability to identify ILO events outside of clinical and laboratory settings. Through gaining ability to at least screen patients via either a questionnaire or a noninvasive physiological field test for later diagnostic confirmation, the scientific community would be better able to quantify the prevalence and public health significance of ILO in terms of all of the domains above. No tool currently exists and future noninvasive technical advances may allow actual diagnosis in the field.

Pathophysiology

A detailed discussion of the pathophysiology of exercise-ILO is beyond the scope of this review. Although there are several theories that attempt to explain the clinical findings of ILO and exercise-ILO, there is little evidence from controlled trials to prove causation for pathophysiological changes. Many of the most widely cited references are cross-sectional or observational. Due to heterogeneity in diagnostic strategies, almost all studies are confined to single centers and many studies pool patients with exercise-ILO with all ILO inducers, limiting generalizability of the findings.

In general, the theories describing exercise-ILO highlight potential predisposing factors rather than the specific mechanisms or etiology underlying the final common pathway of glottic adduction and supraglottic narrowing. One theory in explaining ILO speculates that sensitization of the larynx by a variety of irritants, including laryngopharyngeal reflux,
predispose to inappropriate glottic adduction as an overactive protective reflex [18]. Although certain athletes, particularly indoor swimmers, may note pronounced symptoms only in certain presumed irritant-laden locations, a direct physical irritant-effect and laryngeal hypersensitivity have never been documented scientifically in exercise-ILO or ILO in general. The role of gastroesophageal reflux was concluded to be less important in exercise-ILO than in other forms of ILO in one retrospective study [17]. The role of underlying behavioral predisposition as a factor in exercise-ILO has been discussed in pediatric and adult exercise literature for decades, particularly in competitive sports where emotional stress is identified, although the specific causal mechanisms are poorly understood [19,20]. Formal prospective characterization in 45 adults with ILO via Minnesota Multiphasic Personality Assessment-2 demonstrated a group pattern, referred to as the conversion-V pattern, which is commonly seen in functional somatic syndromes (although subgroup analysis in exercise-ILO patients was not reported) [21]. In a cohort of patients with exercise-ILO, – 25% had documented psychiatric diagnoses [17]. Dysfunctional increases in muscle tension have been proposed as possible contributors to ILO [22]. Finally, supraglottic tone has been more recently associated with glottic adduction in exercise-ILO [23]. At a mechanistic level, however, it is still unclear if, and exactly how, these two findings interrelate.

Clinical presentation

The clinical presentations of exercise-ILO differ and has been reviewed previously in this journal [7,24]. In the clinic setting, history is the most informative element of the presentation and nuances are described in detail below. On history, dyspnea is reported as the most commonly reported symptom in 73% of ILO patients followed by wheeze (36%), stridor (28%), cough (25%), chest tightness (25%), throat tightness (22%), and changes in voice (12%) in ILO with unspecified inducers [25]. The time course of symptoms in relation to exercise intensity may be helpful. Although it has never been characterized at a quantitative level, it is felt that exercise-ILO is most prominent at high exercise intensities and resolves relatively rapidly (over a few minutes) when compared to other causes of dyspnea. A refractory period, defined as a period of time over which a repeat challenge causes a smaller quantity of symptoms or obstruction, is not present characteristically with exercise-ILO but is often present in exercise-induced bronchospasm (EIB) [24]. Hypoxemia and cyanosis are rare in cases of exercise-ILO (and should lead to other diagnostic considerations), but pallor, lightheadedness, and paresthesias may occur [24]. These findings have been speculated to result from either hyperventilation (despite partial obstruction) or changes in negative intrathoracic pressure leading to cerebral hypoperfusion causing tissue hypoxia. However, intrathoracic pressure measurements during different magnitudes of exercise-ILO have not been investigated.

Our clinical experience suggests that the history can notably be guided or misguided by use of the word ‘wheeze’ by clinicians or patients. Noisy breathing is characteristic of obstruction to air flow in ILO. More specifically for most practitioners, ‘wheeze’ implies lower airway limitation on exhalation as identified in asthma (although wheeze can also be heard on inspiration in asthma). Frequently, inspiratory respiratory noises attributable to the upper airway are stridulous but may be misinterpreted as ‘wheeze’. The incorrect assumption that patients appropriately understand the terms will generally lead to incorrect diagnoses, specifically asthma. Clinicians may avoid this misunderstanding by asking patients to reenact characteristic respiratory noises during exercise, which at times is not possible.

Our clinical experience also suggests that symptom perception and reporting may be strongly influenced by exercise type and intensity, severity of glottic and supraglottic narrowing, age, and behavioral makeup. Exercise intensity is an important determinant of symptom reporting because patients express their overall limitation in terms of disease impact on performance. The severity of obstruction is important because, intuitively, more severe obstruction likely presents with more severe limitation. The age of the patient is important because it affects symptom perception and reporting as well as developmental variables inherent in the anatomy of the upper airway. It is critical to consider behavioral factors to contextualize the clinical presentation in exercise-ILO because different patients may describe the same phenomenon with a range of severity, from unspecified performance decrement to catastrophic medical emergencies. Anxiety (trait anxiety, state anxiety, and anticipatory anxiety) and emotional stress (eg, fear of failure, fear of success, social/familial expectations) may contribute to the symptoms experienced [20].

In general, resting physical examination findings are not highly specific for ILO [24]. Auscultation over the neck and trachea should always be performed during pulmonary evaluation. Resting physical examination can lead to alternative or coexisting diagnoses, if stigmata of allergic disease, auscultated wheeze, fixed stridor, pathologic murmurs, gallops, or evidence of systemic disease are present. While patients are exercising, some experienced clinicians can distinguish the anatomic region of turbulence by simultaneously auscultating the neck and chest [26]. It is the authors’ opinion that sound analysis with recording stethoscopes may be helpful in the future.

Differential diagnosis

When considering the differential diagnosis for ILO and diagnostic evaluation from the perspective of the primary care clinician, there are two distinct groups of patients that differ in terms of obstruction severity and symptom perception. The first group includes patients with specific symptoms that indicate the source of clinical symptoms to directly pertain to the upper airway (proximal to sternal notch). The second group is individuals with nonspecific respiratory symptoms such as dyspnea or exercise intolerance in whom the upper airway needs to be considered in the differential diagnosis [14].

In patients with symptoms attributable to the upper airway including hoarseness, voice changes, resting stridor, resting cough, and/or dysphagia, clinicians must consider a range of upper airway disorders (Table 3). Dysarthria, hypernasality, dysphagia, altered mental status, or generalized movement abnormalities should be fully evaluated for alternative
The Physician and Sportsmedicine Downloaded from informahealthcare.com by National Jewish Medical & Research Center on 02/03/15

Lower airway diseases

<table>
<thead>
<tr>
<th>Airway location</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal disorders</td>
<td>Neurogenic</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocal fold disorders</td>
<td>Vocal fold paralysis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vocal fold paresis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheobronchial disease</td>
<td>Foreign body</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower airway diseases</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

diagnoses of ILO when present. Neurological disease, while excluded in the formal definition of ILO, can increase laryngeal hypersensitivity which can cause or exacerbate the symptoms that mimic ILO.

In those patients with nonspecific respiratory symptoms such as exertional dyspnea, the primary diagnoses to be considered in the exercise-ILO differential are asthma and EIB, with EIB likely occurring much more frequently. In a 2002 study of 105 active duty military personnel with exertional dyspnea, the predominant diagnoses were asthma or EIB in 47% of the cohort, whereas ILO was the next most common diagnosis in 10% of patients [13]. However, there is no specific set of symptoms that can reliably differentiate the two disorders [20,26]. Approximately one-third of patients with ILO have been previously diagnosed with asthma due to the similarity of clinical symptoms [27].

Based on symptoms and physical examination findings, consideration may be given for potential underlying cardiac disorders. In a younger population presenting with nonspecific dyspnea, evaluation may reveal evidence of myocarditis, hypertrophic cardiomyopathy, anomalous coronary arteries, or long QT syndrome. In an older population above the age of 35 (based on presenting symptoms), other conditions such as coronary atherosclerosis, dilated cardiomyopathy, congenital heart disorders, such as bicuspid aortic valve, and infiltrative heart disease can be considered [28].

Diagnostic evaluation

There is no single diagnostic algorithm which will apply to all patients with exercise-ILO. The authors recommend a spirometry with bronchodilator testing as a diagnostic tool for dyspnea evaluations. The presence of baseline obstruction or reversibility (a 12% increase in forced expiratory volume in 1 second) may be suggestive of underlying asthma. However, measured obstruction does not exclude exercise-ILO [15].

The inspiratory limb of a properly acquired flow-volume loop might suggest fixed or variable upper airway obstruction. If obstruction is not present on spirometry, confirmation of airway hyperreactivity can be evaluated with bronchoprovocation testing (methacholine or mannitol). Methacholine challenges have been noted in the literature to demonstrate false-positive results (for bronchospasm) in patients with simultaneous ILO [29]. Various procedures such as testing for atopy, impulse oscillometry, exhale nitric oxide, or spumum eosinophilia may also suggest asthma. However, there have been no prospective studies capable of differentiating asthma from ILO, based on these testing procedures.

A comprehensive laryngeal evaluation including laryngoscopy (ideally with stroboscopy) can identify and exclude confounding diagnoses (including laryngeal and subglottic masses, irregular anatomy, vocal fold motion/vibration anomalies, and evidence of impaired swallowing function) before establishing a diagnosis of ILO. In some cases, adjunct studies such as computed tomography/magnetic resonance imaging of the chest/neck may be indicated to rule out tracheal disorders (Table 3). There is no role for imaging or blood gas analysis in the confirmation of exercise-ILO, although these modalities can be used to evaluate other diagnoses in the differential.

As symptoms and physiological abnormalities are often not present at rest, provocation challenges are often necessary to reach a definitive diagnosis. Provocative challenges of sufficient intensity to provoke symptoms are not generally feasible in the initial clinical visit (highlighting the importance of the history). However, in an age where portable video recording devices are widespread, the authors recommend review of videos obtained during exercise to characterize events and supplement the history. Audio tracks can characterize the difference between inspiratory and expiratory noises suggestive of stridor or wheeze. Pallor and cyanosis can be evaluated grossly with videos. Review of the accessory muscle use pattern can also differentiate inspiratory from expiratory distress.

Laboratory provocation challenges are feasible at many centers. At most referral centers, it is possible to directly observe the vocal folds and supraglottic structures with flexible laryngoscopy after exercise challenges. Whereas exercise can induce either EIB or exercise-ILO, inspiratory stridor, rapid symptom resolution after exercise, and/or lack of response to inhaled β-agonists may indicate the presence of exercise-ILO.

For reasons related to feasibility and tradition, laryngoscopy had historically been performed immediately after an exercise challenge. However, in the past decade, several authors have advocated the use of continuous laryngoscopy during exercise as the preferred means to identify ILO [30-32]. This is a procedure which features an exercise challenge with a flexible
laryngoscope mounted to a patient for the duration of the challenge. The advantage of the continuous approach is that glottic and supraglottic movements can be characterized over time, with subtle changes more easily noted and contextualized. This method may decrease the likelihood of a false-positive examination because the possible initial protective reflex and associated glottic changes induced by laryngoscope placement are temporally separated from exercise symptoms. This method may decrease the likelihood of a false-negative examination in patients with rapidly resolving symptoms because visualization occurs at peak work capacity (rather than 30 seconds after an exercise bout). Currently, only specialized centers can perform and interpret the procedure. There is also not a large body of literature about normative findings in athlete-specific populations.

Clinicians who perform laryngoscopy for ILO will recognize the challenges in interpretation of images and videos. The same task force which released terminology recommendations has provided guidance with laryngoscopy interpretation [8]. In regard to the laryngoscopic images, the group advocates specific identification of the location of the obstruction as either supraglottic (arytenoid regions, the epiglottis or vestibular folds), glottic (the vocal folds), or both supraglottic and glottic. Additionally, the group advocates specific identification of the phase of the respiratory cycle during which the obstruction is present and should be documented as inspiratory, expiratory, or biphasic. During continuous laryngoscopy, one is able to evaluate the onset of the time course of changes. In these cases, the international task force recommends describing laryngoscopically visible obstruction as either fast onset (from one breath to the next) or slow onset (over several breaths). Finally, the group recommends describing the resolution of the laryngoscopically visible obstruction after cessation of exercise (if the obstruction becomes visible during exposure) as either fast (e.g. within 5 minutes), or slow (e.g. ≥ 5 minutes). If onset and resolution cannot be observed, this should be clearly stated and the reason given.

Table 4. Behavioral interventions for exercise-inducible laryngeal obstruction.

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reassurance and education</td>
</tr>
<tr>
<td>Diaphragmatic breathing</td>
</tr>
<tr>
<td>Relaxation therapy</td>
</tr>
<tr>
<td>Voice therapy</td>
</tr>
<tr>
<td>Respiratory retraining</td>
</tr>
<tr>
<td>Biofeedback</td>
</tr>
<tr>
<td>Attentional training</td>
</tr>
<tr>
<td>Hypnosis</td>
</tr>
<tr>
<td>Cognitive-behavioral psychotherapy</td>
</tr>
</tbody>
</table>

Therapeutic considerations: a team approach

After a diagnosis is suspected or confirmed, treatment of patients with exercise-ILO involves a number of different complementary participants and treatment modalities (Table 4). At this time, there are not clear treatment guidelines for this condition and the following survey of available treatment modalities is provided for clinicians to understand the range and scope of possible therapies.

The diagnosing clinician, whether a generalist, sports medicine practitioner, pulmonary specialist, or otolaryngologist, is central to the treatment process. Clinicians are responsible for educating patients about the nature and severity of exercise-ILO, reassuring patients that they can learn to control their symptoms and treating documented potential contributing comorbidities (including pulmonary disease, rhinitis, gastroesophageal reflux, and dysphagia). Clinicians must be tactful to maintain unbiased interest and nonjudgmental concern, while initially avoiding the discussion of psychiatric diagnoses which may be interpreted as ‘it’s all in my head’, and may be perceived as accusatory and implied malingering [33]. Patients may not follow up on referrals when initially confronted with a functional diagnosis. It should not be presumed that underlying psychiatric disorders, such as somatic symptom disorders, anxiety disorders, depression, or other psychopathology, are not present in ILO. As noted in the section below, psychotherapy remains an important treatment modality for ILO. Most importantly, the diagnosing clinician sets the expectation that behavioral interventions will be the initial plan for effective treatment, likely with speech-language pathologist or a biofeedback therapist.

Evidence of behavioral interventions

Although behavioral interventions (summarized in the sections that follow) are the mainstay of therapy for exercise-ILO, it is notable that a recent Cochrane review of the treatment of ILO with psychological or behavioral interventions, including speech-language pathology, concluded that there are no prospective, controlled outcome studies that adequately assess the efficacy of any of numerous treatment interventions (Table 5) [34]. This conclusion is based on methodological considerations related to the variability in diagnostic criteria, biased patient selection, variability in treatment approaches across centers, lack of randomization, and the lack of control treatments, which preclude definitive support or rejection of specific therapies [34]. Despite the lack of randomized, placebo-controlled evidence, many modalities (which generally share common techniques

Table 5. Summary points.

A new nomenclature, using the term ‘ILO’ is advocated by an international task force to replace terms such as ‘vocal cord dysfunction’, ‘paradoxical vocal fold motion’, and ‘laryngomalacia’

Exercise-ILO is suggested by rapidly occurring and rapidly resolving dyspnea, often with noisy breathing (e.g. stridor)

Exercise-ILO does not explain resting imaging or blood gas abnormalities

Primary care physicians may grossly examine videos of patients exercising in the field to supplement the clinical history and examination

Continuous laryngoscopy during exercise is an emerging diagnostic strategy to definitively confirm the diagnosis of exercise-ILO

Several behavioral therapies, including speech therapy, biofeedback and self-hypnotherapy, and psychotherapy, are used in treating exercise-ILO

Abbreviations: ILO = Inducible laryngeal obstruction.
including relaxation, diaphragmatic breathing, distraction, and attention training) are employed at referral centers.

General considerations for behavioral therapies in exercise-ILO

An initial behavioral consultation for treatment of exercise-ILO (with a speech-language pathologist, biofeedback specialist, or other behavioral specialist) may consist of 1) a review of patient symptoms, comorbidities, and triggers; 2) identification of personal impact of disease as well as goals for improvement; 3) education about the upper airway and exercise-ILO; and 4) instruction in techniques to manage and reverse symptoms. From a process perspective, the interaction should complement and build off the initial and follow-up clinician visits.

Speech-language pathologists and other behavioral therapists generally attempt to decrease the frequency of breathing maneuvers and upper body tension by instructing patients to relax their shoulders and focus on diaphragmatic breathing prior to implementing specific breathing techniques. Tactile biofeedback, via the use of an elastic band placed around the upper abdomen or a tissue box on the abdomen of a supine patient, can improve diaphragmatic breathing support while resting and exercising.

Speech-language pathology intervention

Speech-language pathologists convey knowledge of upper airway mechanics to improve respiratory symptoms in patients. They can provide patients with a visual overview of the anatomy and physiology of the head and neck, focusing on the protective role of vocal folds in coughing, throat-clearing, breath-holding, and swallowing. They also can help patients gain insight into control measures once environmental intolerances have been objectively identified, which may decrease the likelihood of an attack [35]. The ILO literature is unclear as to which intolerances in an individual may result from cellular inflammation/injury or psychological factors, or a combination.

A variety of breathing techniques have been reported as successful, related to voice therapy and respiratory retraining [10]. As described above, there are not adequate, well-designed prospective studies evaluating the efficacy of any therapeutic interventions. Many of the specific breathing techniques, including pursed lip breathing, are hypothesized to increase the likelihood of inspiratory vocal fold abduction during exercise. Considering another disease model, patients with chronic obstructive lung diseases (who often perform pursed lip breathing techniques) demonstrate expiratory glottic adduction, however [36].

Follow-up appointments are advocated to reinforce previously taught techniques and because clinical response has been linked to the quantity of follow up [17]. These visits can focus on breathing technique mastery, desensitization to specific exercise-related events, and customization breathing techniques.

Biofeedback

Biofeedback via several techniques has been used to treat exercise-ILO [20]. Control of physiological mechanisms associated with autonomic arousal, electrodermal reactivity, peripheral vascular finger temperature, muscle tension, and electromyography have been validated to be effective self-regulation techniques to mediate relaxation [37]. Laryngeal image biofeedback was first described in 1987, showing that subjects could have some control of their vocal cords, but no exercise-ILO subjects were studied [38].

Hypnosis

Anbar and Hummell employed self-hypnosis, defined as an altered state of consciousness useful in altering thoughts, feelings, expectations, attitudes, behavior, and perception, to treat dyspnea in adolescents without documented pulmonary disease [39]. In a study of self-hypnosis with a cohort of heterogeneous pulmonary conditions, including 29 patients with ILO (exercise-ILO was not specified), symptom resolved for 11 and improved for 9 others after a single hypnosis session [40].

Attention training

Attention training is a self-regulation technique common to many forms of meditation. The purpose is to achieve a state of physiological homeostasis or relaxation. The mental imagery is not content-based, as it is in hypnosis in which images of pleasant places are retrieved, or in autogenic biofeedback training. One structured method of attention training is Open Focus Attention Training [41]. Open Focus Attention Training in conjunction with short-term psychotherapy was successful in the treatment of two of three patients with ILO attributed to reactions to environmental agents [42].

Psychotherapy

Psychotherapy remains an important treatment modality for ILO, particularly in patients with a history of past or present psychological or stress disorders. During medical or behavioral consultation, the opportunity may arise for discussion of referral to a psychologist or psychiatrist. Specific treatment by performance psychology specialists has been used as well in the treatment of exercise-ILO. Cognitive-behavioral and cognitive therapies are considered the treatment of choice for functional somatic syndromes [43]. Psychotherapy and the use of medication can also be essential in the treatment of comorbid depression spectrum and anxiety spectrum disorders.

Future directions: focusing on gaps and current knowledge

Exercise-ILO is an important condition but has been a challenge to study for several reasons. Moving forward, the authors feel that agreement on clinical trials infrastructure and methodology will enable research into disease mechanism and therapeutics.
The most basic step is to utilize agreement in terminology. As described previously, in 2014, an international task force reached consensus in the terminology of exercise-ILO. With time, cross-specialty and cross-institution education and collaboration in regard to study of exercise-ILO may improve due to this agreement.

Another basic step is to achieve agreement in diagnostic criteria for both clinical and research purposes [25]. This is challenging for several reasons. Importantly, exercise-ILO cannot always be reproduced in a clinical or laboratory setting. Moreover, its presence, duration, and severity vary across exercise modes, exercise intensities, personal behavioral traits, and situational variables inherent in testing scenarios. Definitive documentation requires exercise testing equipment and flexible laryngoscopes, which are presumably only available to a minority of practitioners who treat patients ILO. Symptom duration is particularly important because it determines whether direct visualization of the larynx must occur during rather than after challenge testing [30]. Finally, there is no consensus (or data) on the severity of observed obstruction which defines physiological significance or disease [32].

Once there is clear agreement to terminology and disease definition, the scientific community will need to refine disease outcome measures, which will ultimately be used to evaluate interventions. In 2014, the Dyspnea Index, which is a metric used in evaluating patients with many types of upper airway obstruction, was published as potentially helpful for use in adolescents with exertional dyspnea attributed to exercise-ILO (after history, physical examination, and resting laryngoscopy) [10]. It is not clear if this metric will have the test properties required to be useful in clinical trials, but clinicians can decide if this or other indices are presently helpful in tracking patients over time. In addition to symptom-based metrics, there is a need for developing physiological metrics of disease severity for use in a clinical trials setting. This includes, but is not limited to, quantitative measures of laryngoscopic images [12,32].

In addition to standardized metrics of clinical outcome, there is a need for standardized metrics of conditions which may predispose or modify exercise-ILO in order to accurately phenotype patients. Variables will be challenging to qualify in terms of validity and relevancy and to quantify in terms of impact on phenotypes. Furthermore, phenotypes may be affected by a variety of other factors that we do not yet understand.

The final elements which require standardization before the field can progress are the many behavioral and surgical interventions used for treating exercise-ILO. As noted previously, a 2013 Cochrane review, which concluded that there had been no high-quality clinical trials for this condition, highlighted the fact that behavioral intervention begins with the provider that initially suspects ILO [34]. To avoid bias, researchers must closely control the flow of information to patients in order to ensure a consistent level of baseline knowledge across patients before interventions are implemented. Furthermore, although many clinicians feel that speech therapy is the first line of therapy, there is in fact huge heterogeneity in clinical practice across speech-language pathologists and centers. Other clinicians may prefer psychotherapy or other behavioral interventions including specific relaxation and breathing techniques, but these interventions must also be taught in a uniform manner in the trials setting. Additionally, in order to assess the efficacy of any behavioral technique, one must assess the efficacy of the teaching process in addition to taught content. In certain centers, surgery has been advocated for ILO [44]. As with behavioral therapies, in order to study the efficacy of the intervention, standardization of patient selection and the procedure must occur. In practice, all of these items are quite challenging to achieve and highlight the difficulty in using clinical populations to study disease.

Through achievement of these steps, it will soon be possible to conduct high-level clinical trials for patients with exercise-ILO. Over time, our understanding of disorder phenotypes, mechanisms, etiologies, and optimum treatment will improve accordingly.

**Summary**

The upper airway has been recognized as a cause of episodic dyspnea for over 100 years and as a cause of exertional dyspnea for ~30 years. Despite the long-standing recognition, there has been minimal progress in defining the epidemiology, etiology, pathophysiology, optimal diagnostic strategies, and optimal treatment strategies of exercise-ILO because there is notable heterogeneity in terminology, diagnostic techniques, and outcome measures within and across centers. Recent advances aim to solve these problems, including a new nomenclature matrix advocating the term exercise-ILO and a new diagnostic technique called continuous laryngoscopy during exercise. Although current behavior interventions are the mainstay of therapy, in 2014, experts in the field hope to improve diagnostic techniques and improve targeted treatment in the years to come leveraging the advances described above.

**Acknowledgments**

The authors acknowledge all contributors in the Upper Airway Working Group, based at National Jewish Health, for their insights into this and future projects. The authors also thank George Zeman, Valerie Keever, Mark Fleming, Dave Gurka, and Lisa Fails for their support of continuous laryngoscopy during exercise as well as D Sundstrom and Dusty Christian for their assistance in coordinating the research group.

**Declaration of interest:** M. J. Morris has been a speaker for Boehringer-Ingelheim. K. L. Christopher is on the advisory boards for ILO International Task Force, National Association for Medical Direction of Respiratory Care, and the American Association for Respiratory Care, and is employed by and holds a patent with CS Medical, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
Inducible laryngeal obstruction during exercise

References