

Working Towards a Common Transatlantic Approach for Evaluation of Exercise-Induced Laryngeal Obstruction



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KEYWORDS

- Exercise-induced laryngeal obstruction (EILO)
- Continuous laryngoscopy during exercise (CLE)
- Exercise-induced bronchoconstriction (EIB)
- Exercise-induced inspiratory symptoms (EIS) • Vocal cord dysfunction (VCD)

KEY POINTS

- The history is the key to a correct exercise-induced laryngeal obstruction (EILO) diagnosis, with inspiratory symptoms presenting during ongoing exercise and resolving within a few minutes after exercise termination.
- Exercise-induced inspiratory symptoms (EIS) have multiple causes but are most often related to various forms of laryngeal obstruction; if so, the condition is labeled EILO.
- At present, no tools exist that can diagnose EILO at rest.
- Laryngoscopy performed as symptoms evolve, through the use of a procedure known as continuous laryngoscopy during exercise, is pivotal to patient workup.

Exertional dyspnea is a common presenting symptom among patients of general practitioners, respiratory specialists, allergists, otolaryngologists, cardiologists, and sports medicine specialists. The symptom complex is important as symptoms per se, as manifestations of systemic disease, and as a potential contributor to a sedentary lifestyle. Exertional dyspnea can be caused by a variety of conditions rooted in

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dysfunction of multiple organ systems and can be described variably by patients across etiologies.¹ Treatment depends on the cause of symptoms and may be simple, as in cases of mild exercise-induced asthma, or complex, as in cases of anemia caused by oncologic processes.

A malfunctioning larynx can be a source of exertional dyspnea. The larynx serves a variety of functions, and, in addition to moving in a precise manner to generate voice, it must accommodate between 100 L and 280 L per minute of airflow during intense exercise in adolescents and adults.² Exercise-induced laryngeal obstruction (EILO), the consensus term for the condition previously known as vocal cord dysfunction and paradoxical vocal fold motion, is defined by inappropriate narrowing of the larynx during high-intensity exercise.³ First described in the 1980s as a mimic of asthma, EILO is an important condition for allergists and pulmonologists to consider because it is common in specific populations.⁴ Recent studies from Scandinavian countries have highlighted the high prevalence of EILO in young and otherwise healthy young people, 5.7%⁵ and 7.5%⁶ of unselected adolescents in Uppsala, Sweden, and Copenhagen, Denmark, respectively. Studies of soldiers and athletes in stressful situations have revealed even higher rates.^{7,8}

Given this high prevalence of EILO as well as its frequent misdiagnosis of asthma and the international effort stressing the importance of regular exercise for general health,⁹ there is a need to develop diagnostic recommendations for the diagnosis of EILO.¹⁰ A process to establish definitive diagnoses of EILO also serves other purposes. At an individual patient level, there is value in distinguishing EILO from asthma or other conditions to minimize unnecessary therapies, something commonly noted by investigators and also by the general press.^{10–12} There is also value in distinguishing EILO patients from patients with other forms of inducible laryngeal obstruction (ILO) because there is important literature devoted to psychopathology in patients with resting symptoms, sometimes stigmatizing the diagnosis.^{13–15} At the level of the medical provider community, streamlined recommendations are important because there is variability in terms of awareness of EILO across provider populations. As highlighted during discussions at the first international EILO conference in Bergen, Norway, April 2017, there is a perceived under-awareness of EILO within certain provider communities, but there is also a perception of EILO overdiagnosis which has led to EILO fatigue in other provider communities.

The recommendations for exertional dyspnea evaluation and EILO diagnosis presented in this review consider differences in perspective across continents and have incorporated feedback from providers across a variety of medical specialties (including generalists, allergists, pulmonologists, pediatricians, otolaryngologists, cardiologists, and sports medicine providers). Each of these perspectives is important because it is reasonable to hypothesize that providers of different backgrounds and specialties may differ in their experience with the presenting complaint, framework for considering the complaint, and interest in relevant differential diagnoses. Their experience may also vary with respect to their access to and experience with diagnostic testing and therapeutic interventions.

These recommendations incorporate those of consensus opinion panels convened to address the topic.^{3,16} The review considers aspects of the presenting history with physical examination as well as the diagnostic work-up. Because the study of EILO is in its infancy when considered against exercise-induced asthma and exercise-induced bronchoconstriction (EIB), this article attempts to qualify recommendations with comments about literature strength in the area.

PRESENTATION AND HISTORY

Patients with EILO generally present with exertional dyspnea, although there is not a specific subset of symptoms that clearly defines a high likelihood of EILO, which has been validated across age, gender, race, ethnicity, and culture. Nonetheless, for decades, investigators have attempted to differentially characterize the prototypical symptoms in isolated EILO from those of patients with other conditions—especially isolated EIB.¹⁷

The concept of exercise-induced inspiratory symptoms (EIS) has been used in the literature as an attempt to provide a label for the set of symptoms exhibited by patients with upper airway obstruction (Fig. 1).^{18,19} EILO patients often qualitatively describe their dyspnea as a distressing “wheeze,” something that occurred in 1 of the first publications on EILO,⁴ despite that the prototypical EILO symptom is inspiratory stridor. Symptoms often occur during intense exercise, at times during episodes of exercise that are particularly important to the patient, and generally resolve within a few minutes.^{17,20}

Patients may note that environmental conditions, especially temperature extremes, are associated with increasing likelihood of symptoms.⁴ In describing EIS, some investigators have noted descriptions of pain in the chest or throat area as well as associated hyperventilation.²¹ Sometimes this pattern progresses to frank panic reactions, evolving in parallel with increasing ventilatory requirements as the intensity of the exercise increases.^{22,23} The timing of symptoms (within the respiratory cycle, within a given exercise session, and with respect to recovery) is of critical importance when distinguishing EILO from asthma, with EILO symptoms typically starting in association with very intense exercise and resolving within a few minutes of exercise termination.²⁴

In contrast, many patients with exercise-induced bronchospasm with asthma present with a long-standing history of known asthma.²⁵ Rather than describing discrete events with a clear beginning and end, these patients often describe shortness of breath with an onset after prolonged exercise and resolution remote from exercise

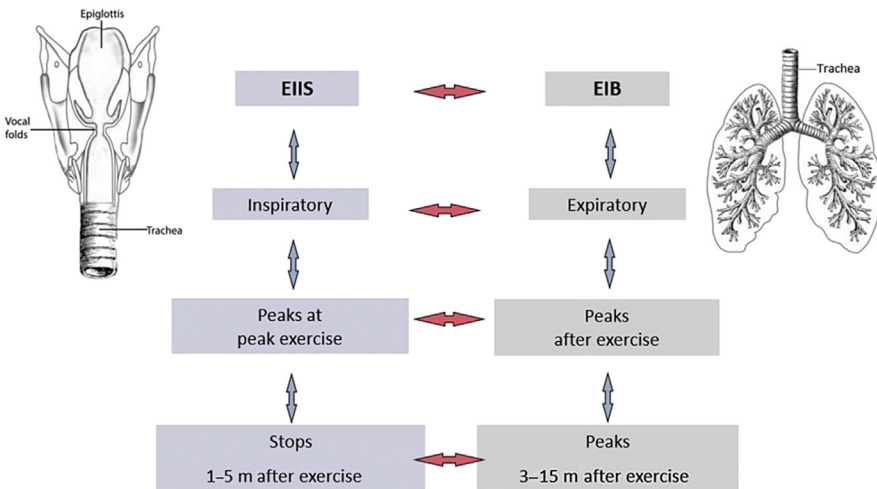


Fig. 1. Characteristics of EIS versus symptoms of EIB. (From Røksund OD, Heimdal JH, Clemm H, et al. Exercise inducible laryngeal obstruction: diagnostics and management. *Paediatr Respir Rev* 2017;21:87; with permission.)

termination.^{26,27} Cough is frequently associated, as is chest tightness. Audible respiration is often not perceived.²⁰ In the authors' experience, distress is frequently not described with the exception of severe events.

In the authors' experience, patients with exertional dyspnea, especially adolescents, sometimes struggle to fully characterize their symptoms at an initial visit. Some present with a vague sense of breathing problems that occur in relation to exercise, feeling unable to breathe and not "get enough air," particularly during intense exercise. Characterizing dyspnea within the respiratory cycle can be challenging, particularly for patients with expiratory limitation. One of the initial challenges faced by clinicians working with patients with exertional dyspnea is establishing a characteristic history without the use of excessively leading questions.

The clinical history may be more complicated to disentangle in reality than the impression conveyed in **Fig. 1**, which is presented as a way of distinguishing prototypical descriptions of EILO and EIB. Some of the prototypical descriptions of EILO may be based on the findings in seminal literature, which did not rely on direct visualization for diagnosis.^{20,28,29} This approach also intentionally looks past other diseases that affect the cardiorespiratory system. As a clinician, it is important to acknowledge that there may be multiple phenotypes of both EIB and EILO, each with slightly different patient descriptions of symptoms. It is also important to consider that EILO and EIB may coexist, clouding the presentation.^{5,10,17,20,28,30}

DIAGNOSTIC EVALUATION OF EXERTIONAL DYSPNEA WITH A FOCUS ON EXERCISE-INDUCED LARYNGEAL OBSTRUCTION

The authors agree with recent literature^{3,19} and strongly recommend reserving a diagnosis of EILO for cases supported with direct visualization during characteristic events (as opposed to relying only on patients' histories or responses to therapeutic trials).^{29,31} This advice is in line with published diagnostic recommendations for EIB.²⁵ This opinion is supported by diagnostic algorithms developed for military personnel in whom misinterpreting respiratory symptoms can be fatal.³²

The likelihood of an EILO diagnosis varies, however, with clinical presentation and likely changes as other causes of dyspnea are identified. For this reason, rather than recommending definitive testing all patients with exertional dyspnea, the authors recommend limiting definitive testing to those in whom a reasonable clinically assessed pretest probability of EILO exists.

SPIROMETRY AND BRONCHOPROVOCATION TESTS

Spirometry is commonly available to providers across several medical specialties. Early literature suggested that abnormal resting flow-volume loops in patients with EIS were suggestive of a diagnosis of EILO.^{4,14,20,28} Other literature notes, however, suboptimal specificity of resting inspiratory loop analysis as a predictor of EILO.^{20,28,33,34} According to Christopher and Morris,²² the most common causes, for example, of resting inspiratory loop truncation are inadequate instruction, suboptimal effort, and inability to perform the procedure, often reflected in poor repeatability.^{35,36} Spirometry may also lead to falsely negative findings and the sensitivity regarding identification of patients with EIS is low.^{7,20,28,33} Various cutoff levels for inspiratory versus expiratory flow ratios have been suggested, with no validated consensus obtained.^{14,20,33,37} Thus, the literature as a whole does not support the notion that EILO can be confirmed or rejected by resting spirometry.

Spirometry is nevertheless important in patients with EIS because it is central to the evaluation of asthma, subglottic stenosis, airway malacia, or intrathoracic

compressions of various forms. Spirometry is also useful in the assessment of other chronic diseases. Distinct and fixed flattening of the inspiratory and/or expiratory parts of the flow-volume loops in patients with EIOS should incite further assessment.²²

Spirometry can be combined with direct and indirect bronchoprovocation challenges in the assessment of asthma, but these challenges do not provoke characteristic events of EILO. It has been shown that bronchoprovocation challenges with either a methacholine or mannitol did not correlate with EILO as detected via continuous laryngoscopy during exercise (CLE test).³⁸ Most investigators have concluded that methacholine challenge tests are of little value to distinguish EILO from asthma, particularly because the 2 conditions are not mutually exclusive.^{20,22,28,39} Spirometry during exercise, using exercise flow-volume loops, has been considered a potential diagnostic modality for EILO. Theoretic benefits of the modality include the noninvasive nature of the technique. At the current time, the technique has not been validated nor have threshold criteria been set to define the condition. It is unlikely that exercise flow-volume moves will become sufficient for the diagnosis of EILO for reasons related to interpretation of the test. Flow-volume loops change dramatically over the course of incremental exercise. Additionally, there are reports of patients with normal exercise flow-volume loops occurring simultaneous to symptoms, audible stridor, and the visualized findings of EILO.⁴⁰

Currently, there is no evidence to suggest that other noninvasive techniques are useful to positively confirm diagnoses of EILO. Although impulse oscillometry has been hypothesized as having a potential role in the evaluation of exertional dyspnea in select cases, to the authors' knowledge, there has never been a case of EILO specifically diagnosed by impulse oscillometry.⁴¹⁻⁴³

RESTING LARYNGOSCOPY

Although resting laryngoscopy can detect many upper airway lesions that are present at rest, there is not a role for this procedure in the definitive diagnosis of EILO because the changes seen in EILO are simply not present at rest.^{23,24}

EXERCISE LARYNGOSCOPY

In the past few decades, postexercise (or a combination of preexercise and postexercise) laryngoscopy has been reported as a potential diagnostic technique for EILO.⁴⁴ Although this procedure can be performed in many settings and can detect EILO in some cases, sensitivity of the procedure is not ideal given the inherent time delay between exercise termination and laryngoscope placement, even in the most ideal circumstances.^{18,24}

CONTINUOUS LARYNGOSCOPY DURING EXERCISE

CLE is a procedure that allows laryngeal visualization via a held or fixed laryngoscope before, during, and after exercise.²³ The method has been described as easy to perform and well tolerated at centers with experience, even in young children.^{18,19,45} CLE has been featured in several recent publications.^{5,6,8,18-20,28,45-50} There are clearly logistic challenges to performing the procedure from a technical perspective. There are incremental improvements, however, in image acquisition compared with resting and postexercise laryngoscopy, specifically related to linking data acquisition to the exact time of symptom generation. A task force representing the European Respiratory Society (ERS), the European Laryngological Society (ELS), and the American College of Chest Physicians (ACCP), recently published a consensus document

related to diagnostic considerations in ILO from all causes, including EILO.³ In this document, a central principle in ILO diagnosis involves visualization during an episode of ILO. For this reason, CLE is identified as the preferred diagnostic technique for EILO. The suggested role played by CLE in the work-up of EIS is depicted in Fig. 2.

PROCEDURAL CONSIDERATIONS

As a minimum requirement, a laryngoscope should be in place throughout the complete exercise session, which should be designed to reproduce characteristic field

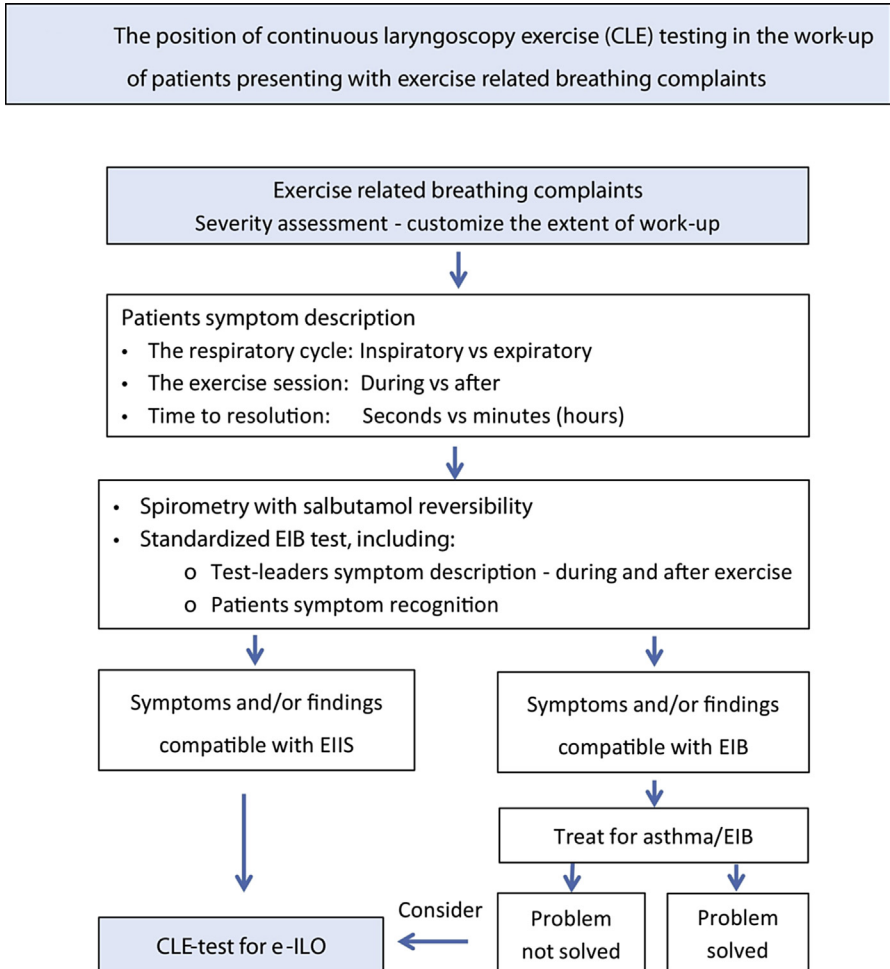


Fig. 2. Work-up should be customized to the level of complaints but should always involve a thorough symptom description. Spirometry, salbutamol reversibility, and a standardized test for EIB are logical second steps. The EIB test should always include a respiratory technician's description of breathing patterns and symptoms during and after the test and a patient verification that the symptoms perceived during the test were similar to those that incited the work-up. EIS during testing without findings in the larynx must incite further work-up. (From Røksund OD, Heimdal JH, Clemm H, et al. Exercise inducible laryngeal obstruction: diagnostics and management. *Paediatr Respir Rev* 2017;21:88; with permission.)

symptoms as defined by the patient. The findings can be recorded for documentation and later review and analysis. A CLE setup can easily be combined with synchronized acquisition of cardiopulmonary exercise data and external video and breath sound recordings of the patient that can then be merged into 1 digitalized file.²³

Exercise Mode

When performing CLE, selection of an exercise mode is an important consideration. Treadmill running, ergometer cycling, rowing, stair climbing, and swimming have all been used to reproduce EIS in a diagnostic setting.^{20,23,46,49,51–53} Ideally, the mode, protocol, and intensity of exercise should be tailored to the individual patient, based on triggers identified from the medical history, as described in rowers by Panchasara and colleagues⁵² and in swimmers by Walsted and colleagues.⁵³ In routine clinics, there must be compromise but at minimum ensuring that exercise continues to exhaustion or to intolerable symptoms. In most young people, treadmill exercise is a more provocative respiratory stimulus than cycle ergometry.⁵⁴ Tervonen and colleagues⁴⁶ used a stationary bicycle and were unable to reproduce symptoms in 50% of patients with EIS and made laryngeal findings in 30%. Some of the inherent environmental limitations present in hospital settings could be overcome by field testing. Although conceptually possible, field testing for EILO has not yet been reported from studies.

Protocol Considerations

In most publications featuring CLE, incremental exercise protocols have been used to generate symptoms.^{24,46} Incremental exercise protocols are popular in a variety of fields of medicine, in part because they allow for the reproduction of metabolic data in a fairly standardized way across patients. More recently, a high-intensity interval protocol was reported.²⁴ There is no evidence that incremental protocols provide the most provocative respiratory stimulus compared with other protocols with respect to EILO. Although tempting to combine the procedure with provocative challenges for asthma, it is important to consider that EILO and EIB are different conditions, presumably involving different causal mechanisms. For this reason, it is unlikely that the same provocative trigger is most effective for both EILO and EIB.

Data Interpretation: What Is Normal?

During exercise, the larynx normally opens fully and the epiglottis rotates anteriorly toward the base of the tongue,⁴⁹ stretching the aryepiglottic folds, thereby allowing for increased airflow with least possible increase of airflow resistance.⁴⁸ The posterior cricoarytenoid muscle is the only laryngeal abductor, acting in a synchronized manner with and ahead of the diaphragm, ensuring that the laryngeal entrance is wide open when inspiratory airflow commences.^{55–57} Few patients have been studied with the aim of characterizing in detail what should be considered normal laryngeal configuration at peak ventilation. Some data suggest that a slight adduction of the aryepiglottic folds at peak ventilation is normal.^{18,49}

Anatomic Descriptions of Exercise-Induced Laryngeal Obstruction

The anatomy, physiology, nervous regulation, and function of the larynx are complex matters, and corresponding heterogeneities in reported findings are expected. In the largest study of EIS to date, 151 patients were CLE tested with findings compatible with EILO in 113 (75%).¹⁸ Adduction started at a supraglottic level in 109, with later glottic involvement in 88. Medialization of the vocal folds generally was noted

anteriorly. Primary glottic adduction was rare. Corresponding data are reported also by other investigators.^{5,6,8,19,58}

Thresholds of Disease

The specific changes in airflow or the laryngeal aperture that define disease have not been physiologically validated. Regarding the vocal gap, McFadden and Zawadski²⁸ proposed that an adduction exceeding 50% was consistent with EILO. Other investigators have defined EILO in terms of semiquantitative scaling.¹⁸ Importantly, most of the airflow through larynx normally takes place in the dorsal part of the glottic aperture, which is the part initially obstructed by medializing aryepiglottic folds.¹⁸

Reporting Findings

The recent ERS/ELS/ACCP task force report³ requests continuous laryngoscopy to be performed from rest to peak exercise and visual verification of adducting laryngeal structures occurring concomitant to symptoms to assign a diagnosis of EILO to a patient.³ The taxonomy differentiates between 2 categories of EILO—glottic and a supraglottic—and acknowledges that these categories can appear separately or combined. Combined glottic and supraglottic EILO may not be cotemporal throughout an attack, and the taxonomy requests each component be separately described and their temporal relation detailed. These distinctions are certainly of practical importance, because patients with severe collapse of supraglottic structures can be treated by laser supraglottoplasty.^{59–62} These distinctions also lead to realizations that terminology that isolates disease to the level of the glottis (vocal cord dysfunction and paradoxical vocal fold motion) is outdated.^{29,63,64}

Why Has Continuous Laryngoscopy During Exercise Been Slowly Integrated into Clinical Care?

Christopher and Morris²² showed in their review from 2010 that laryngoscopy had not been performed in 38% of 355 assessed articles on ILO (not all exercise induced), with CLE rarely used in the studies cited. There are many factors that may explain some of the reluctance of clinicians and researchers in adopting the testing modality. First, the diagnostic yield reported from studies applying the principles of the CLE in patients with EIS has varied.^{10,18,46} This may be related to the fact that there is likely heterogeneity across populations in terms of the frequency of EIS, the proportion of subjects with EIS struggling with EILO, the expertise of referral centers, and differences in testing environments, protocols, and data interpretation. Second, logistic considerations with regards to space, personnel, and resources may be a deterrent.

AREAS FOR FUTURE GROWTH

Although CLE offers several advantages over other forms of diagnostic testing for EILO, there are still several opportunities for future improvement. There is currently no consensus on testing protocols. There is also no consensus on the findings that define disease, which may vary with body habitus, gender, fitness, or athletic level. Current laryngoscopy analysis is subjective and restricted to relative assessments of the cross-sectional laryngeal size, because this changes from rest to peak exercise. A notable gap in scientific knowledge relates to the poor understanding of normal laryngeal size and function in absolute terms and in relation to features, such as gender, body habitus, physical fitness, and exercise capacity. For example, a similar extent of adduction is likely to have different consequences in a narrow larynx compared with a wide larynx and also in a competing athlete compared with a

sedentary person. Linking laryngoscopy with physiologic data, including pressure gradients, may help define the importance of current laryngoscopy observations of unclear significance.

SUMMARY

EILO is one cause of EIS and it is an important diagnosis due to its high prevalence and the ability to treat the condition. It is not reasonable to rely on the clinical history alone, flow-volume loops, or resting laryngoscopy to define the condition. CLE offers notable advantages over postexercise laryngoscopy in terms of diagnosing EILO. Many facility-specific logistic challenges and questions regarding the interpretation of the data have, however, limited its wide-scale use to date.

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