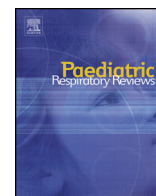


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Review

Exercise inducible laryngeal obstruction: diagnostics and management



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EDUCATIONAL AIMS

The reader will be able:

- To highlight the importance of exercise induced inspiratory symptoms (EIS) in young people complaining of exercise intolerance.
- To emphasize differences between EIS and symptoms of exercise induced asthma.
- To highlight that EIS is usually due to exercise induced laryngeal obstructions (e-ILO).
- To discuss why objective diagnostic test methods are important in patients with EIS.

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SUMMARY

Obstruction of the central airways is an important cause of exercise-induced inspiratory symptoms (EIS) in young and otherwise healthy individuals. This is a large, heterogeneous and vastly understudied group of patients. The symptoms are too often confused with those of asthma. Laryngoscopy performed as symptoms evolve during increasing exercise is pivotal, since the larynx plays an important role in symptomatology for the majority. Abnormalities vary between patients, and laryngoscopic findings are important for correct treatment and handling. The simplistic view that all EIS is due to vocal cord dysfunction [VCD] still hampers science and patient management. Causal mechanisms are poorly understood. Most treatment options are based on weak evidence, but most patients seem to benefit from individualised information and guidance. The place of surgery has not been settled, but supraglottoplasty may cure well-defined severe cases. A systematic clinical approach, more and better research and randomised controlled treatment trials are of utmost importance in this field of respiratory medicine.

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EXERCISE INTOLERANCE; IS IT ASTHMA OR WHAT?

Exercise related breathing complaints are not uncommon in young people, and a scenario all clinicians must be prepared to encounter. Asthma is common in this age group, and a well-established cause of exercise induced bronchoconstriction (EIB), which untreated leads to exercise intolerance [1]. Despite guidelines prescribing objective test methods [2], studies suggest that asthma and EIB are often diagnosed simply based on symptoms [3–5]. However, all exercise related wheeze is not asthma [6], and

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Abbreviations: CLE-test, Continuous Laryngoscopy Exercise - test; EIB, Exercise induced bronchoconstriction; EIS, Exercise induced inspiratory symptoms; e-ILO, Exercise induced laryngeal obstruction; FEV₁, Forced Expiratory Flow in the first second; PCA-muscle, The Posterior Cricoarytenoid Muscle; VCD, Vocal cord dysfunction.

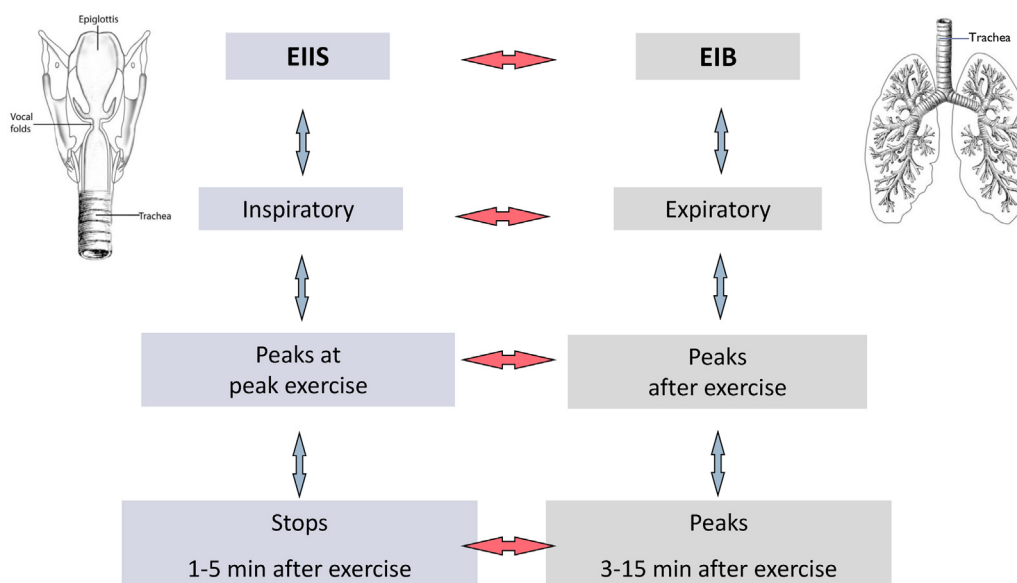


Figure 1. Characteristics of exercise induced inspiratory symptoms (EIIS) versus symptoms of exercise induced bronchoconstriction (EIB).

recent studies have suggested that laryngeal obstruction to airflow might be just as important [7,8].

Physicians' interpretation of symptoms presented by patients will strongly influence subsequent work-up, treatment and follow-up. Principally, airway obstruction inside the thoracic cage produces expiratory symptoms (as in asthma) while obstruction outside the thoracic cage produces inspiratory symptoms. Moreover, EIB is a *response* to increased ventilation induced by high intensity exercise, with symptoms typically peaking 3–15 minutes after stopping [9]. This pattern contrasts symptoms from upper airway obstructions that typically peak *during* exercise or just after stopping (Figure 1). Easy as this might seem, the literature nevertheless indicates that EIB is vastly overdiagnosed in patients with upper airway obstruction [10,11]. One factor that might have contributed to this untenable situation, is the prevailing notion in the literature that upper airway obstruction equals “vocal cord dysfunction” (VCD) and that VCD has been so strongly linked to psychological factors and mental health problems [12–16]. As most patients with exercise related respiratory problems appear as otherwise healthy young people, this misconception might discourage primary care physicians from initiating the correct work-up.

The purpose of this article is to provide state of the art knowledge on diagnostics and management of patients presenting with *Exercise-Induced Inspiratory Symptoms* (EIIS). The article focuses primarily on the role played by the larynx, the highly sophisticated “entrance valve” to the lungs and also the narrowest passage of the airway tree.

METHODS

We searched PubMed for relevant and published research, using the key word “exercise” combined with: Vocal cord dysfunction, paradoxical vocal fold motion, laryngomalacia, laryngeal obstruction, and laryngeal dysfunction. The search was quality-checked by scrutinizing the reference lists of the included studies. Systematic assessment of relevance, design and quality were complicated by large variations (or lack of statements) regarding diagnostic methods, patient inclusion, evaluation and treatment. Particularly, studies tended to mix patients with exercised-induced symptoms and patients with symptoms

presenting primarily at rest; two conditions that are likely to represent different disease domains [12]. Stating clearly in the text when doing so, we also express our personal views and opinions, based on a cumulative experience from more than 1000 patients with EIIS examined endoscopically during exercise over the past 18 years [17].

The joint “Task Force on Inducible Laryngeal Obstructions” established by the European Respiratory Society (ERS), European Laryngology Society (ELS) and American College of Chest Physicians (ACCP) was the first attempt to institute an authoritative nomenclature in this field of respiratory medicine. The statement published in 2015 proposed an umbrella term for laryngeal obstructions; Inducible Laryngeal Obstructions (ILO) causing breathing problems [18]. The inducer of the symptom should precede this term, so in the case of exercise the label becomes e-ILO [18]. The nomenclature underlines what is evident also from the laryngeal anatomy; that obstructions can occur on principally two levels within the larynx: At the supraglottic level due to anteromedial rotation of the cuneiform tubercles or medial movements of the aryepiglottic folds or retroflex repositioning of the epiglottis, or at the glottic level due to vocal fold adduction. Considering the complexity of the larynx, combinations seem plausible.

POSSIBLE AIRWAY ORIGINS OF EXERCISE INDUCED INSPIRATORY SYMPTOMS (EIIS)

EIIS is due to airflow obstruction situated in the upper parts of the airway tree. Based on the presenting symptoms alone, authors have related EIIS to distinct diagnoses, conditions or dysfunction in particular structures, most often the vocal folds. Hence, the term vocal cord dysfunction (VCD) has become widely used. However, the link between EIIS and the vocal folds is based on weak evidence and rarely verified by objective methods [19,20]. The literature reveals a plethora of diagnostic terms used to label relatively similar clinical entities, and vice versa, similar labels have been assigned to conditions that may very well represent different diseases [21]. There has been no agreement on important issues like diagnostic work-up, aetiology, and treatment. This unfortunate situation may be related to heterogeneities within the patient populations, so far not properly acknowledged. Thus, patients

presenting symptoms in different situations (e.g. exercise vs. non exercise) have been lumped together in studies, somehow assuming a similar aetiology [12]. Moreover, patients referred to tertiary level specialised otorhinolaryngology clinics most certainly differ from patients seen in general clinics dealing mainly with diverse respiratory diseases. As research groups will interpret symptoms and findings within the context of their own experience and expertise, there may in fact be no genuine disagreements, only genuine attempts to interpret a heterogeneous reality.

As stated, EIIS is too often confused with symptoms of EIB, often with unfortunate consequences [22,23]. EIB is reportedly common in children, and affects large proportions of children with asthma [24]. Thus, EIB might conceivably be a diagnosis easily resorted to by virtue of a high degree of awareness among physicians and patients. ILO on the other hand, is not as prominent in peoples' thinking, and therefore less likely to be considered. However, if actively searched for, e-ILO is found in high proportions of children with exercise related complaints, with prevalence rates of 7.5% reported from Copenhagen [7] and 5.7% from Uppsala, Sweden [8]. Asthma medication is commonly used by patients with EIIS, often with little or no effect [10,25,26]. In our own study of 151 patients [10], 85% had used asthma treatments, in 64% of these with no effect on exercise related symptoms. It is, however, important to bear in mind that EIB and e-ILO may coexist [8,19,20,25–27].

A SYSTEMATIC DIAGNOSTIC APPROACH TO PATIENTS WITH EIIS

We need a systematic approach in order to disentangle the nature of exercise related respiratory complaints in young people. The present article proposes how continuous laryngoscopy during exercise (CLE) can be used as a diagnostic tool in a clinical context (Figure 2). Three domains are essential in the context of e-ILO: (A) The nature of the symptoms, (B) Lung function findings, and (C) Laryngoscopic findings obtained during ongoing exercise [18,28].

a) The nature of the symptoms

Patients are often unable to account for their symptoms in detail at the first visit. Most present with some form of respiratory complaints occurring in relation to exercise, often made worse by cold climate and also not responding as expected to asthma medications. Three key issues must be clarified regarding symptoms (Figure 1): The position in the respiratory cycle (inspiratory vs. expiratory), and in the exercise session (during or vs. after), and the time to resolution (seconds vs. minutes or hours). Most patients will respond better to these questions if properly informed about what to observe, and then rescheduled for a new interview after another 2–3 weeks of monitoring.

In a test situation, EIB is characterised by changes in forced expiratory volume in first second (FEV₁) occurring from before vs.

Figure 2. The position of continuous laryngoscopy exercise (CLE) testing in the work-up of patients presenting with exercise related breathing complaints

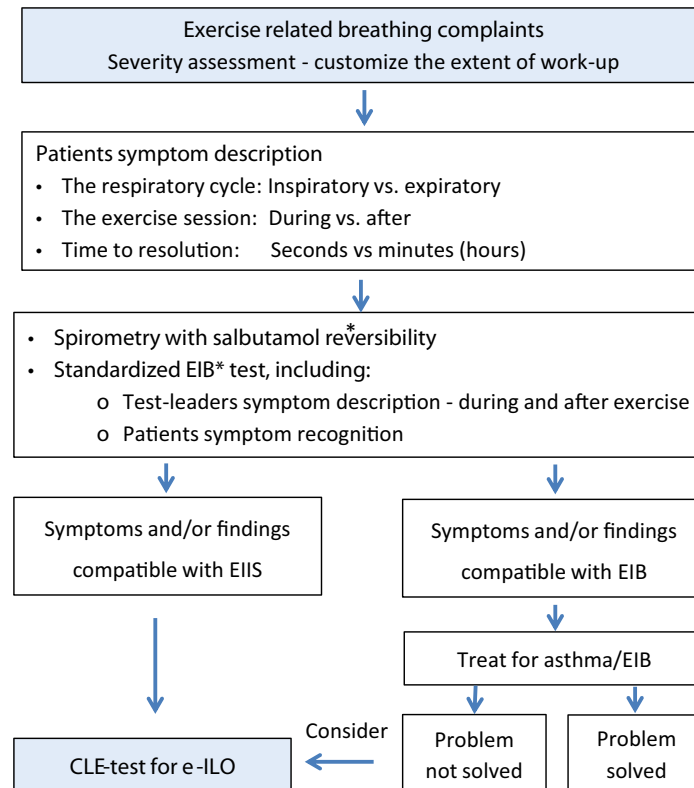


Figure 2. Work-up should be customized to the level of complaints, but always involve a thorough symptom description. Spirometry, salbutamol reversibility assessment and a standardized test for exercise induced bronchoconstriction (EIB) are logical second steps. The EIB test should always include the test-leaders standardized description of breathing patterns during and after the test, and a patient verification that the symptoms perceived during the test are similar to those that incited the work-up. Persistent symptoms without findings must proceed to further work-up.

after the exercise session [29]. The symptoms occur as a response to exercise; i.e. slowly evolving during the first 3–15 minutes after stopping and mainly involving the expiratory part of the respiratory cycle [9]. A correctly performed test for exercise-induced asthma is of diagnostic value also with respect to EIIS, as inspiratory symptoms should be revealed by the high intensity exercise - if present. Breathing patterns and symptoms *during* the test must be recorded, not only changes in FEV₁ after exercise.

EIIS is usually characterised by a fairly typical pattern. The patient starts with increasing breathing difficulties accompanied by a prolonged inspiration with coarse or high-pitched or stridor-like inspiratory breath sounds, sometimes progressing to clear-cut stridor, hyperventilation attacks or frank panic reactions, evolving in parallel with the increasing ventilatory requirements as the intensity of the exercise increases [28,30]. Pain localised to the chest or throat area is relatively common. It is important to remember that EIIS is not a well-defined entity, but rather a series of symptoms that usually occur in sequence, somewhat open to subjective interpretation. A thorough description of observations made during an exercise test should serve to differentiate symptoms of asthma from EIIS.

b) Lung function findings

Several studies have described abnormal resting flow-volume loops in patients with EIIS such as blunted or truncated inspiratory parts of the loops [19,20,22,31]. According to Christopher [28] the most common cause of these findings are inadequate instruction, suboptimal effort or inability to perform the procedure. The repeatability of the findings is poor [32,33] and the sensitivity regarding identification of patients with EIIS is low [19,20,34,35]. Various cut-off levels for inspiratory vs. expiratory flow ratios have been suggested, with no validated consensus obtained [20,31,34,36].

Most authors have concluded that methacholine challenge tests are of little value to distinguish e-ILO from asthma, particularly as the two conditions are not mutually exclusive [19,20,28,37].

Thus, there is no evidence to suggest that e-ILO can be confirmed or rejected by resting lung function tests, and to use flow-volume loops to set specific intrinsic laryngeal diagnoses, such as VCD, seems futile. Lung function tests are nevertheless important, partly as they are needed to exclude EIB in patients with EIIS, and also to indicate the presence of structural central airway obstruction such as subglottic stenosis, laryngo-tracheo-bronchomalacia or intrathoracic compressions of various forms. Distinct and reproducible flattening of the inspiratory and/or expiratory parts of the flow-volume loops in patients with EIIS should prompt further assessment [28].

c) Laryngoscopic findings obtained during ongoing exercise

Visualisation of laryngeal structures during exercise is the “gold standard” for diagnosing e-ILO [18–20,28,38–42]. Christopher showed in a review of 355 articles on VCD (not all exercise induced) that laryngoscopy during ongoing symptoms had not been performed in 38% of patients [28]. Newman wrote that laryngoscopy was diagnostic in only 60% of symptomatic patients [26]. There are several possible explanations for this lack of findings. Importantly, symptoms resembling EIIS may be unrelated to the larynx in an unknown proportion of patients, since obstruction of the trachea or main bronchi can produce symptoms difficult to distinguish from those of e-ILO [10]. Secondly, in most studies laryngoscopies were performed post-exercise, which is a method bound to have a low sensitivity. EIIS usually peaks at maximum ventilation and often resolves rapidly thereafter. As the minute ventilation drops rapidly after stopping exercise [43], the

time required to introduce a laryngoscope in a distressed patient must inevitably lead to false negative tests, and thereby introduce a large bias. Alternatively, the test situation may be inadequate, in that patients are unable to exercise to the level necessary to reproduce their symptoms; e.g. children might find it challenging to bike to peak exercise [38]. A final issue, is the lack of consensus regarding what are normal and what are abnormal findings.

Only by visualising what is taking place in the upper airways in patients with EIIS can their symptoms be properly understood and acknowledged. We therefore strongly recommend that patients who are significantly impaired by EIIS from performing normal physical activities, should be properly examined with laryngoscopy performed continuously throughout a maximal exercise test, from rest to peak exercise.

THE CONTINUOUS LARYNGOSCOPY EXERCISE (CLE) TEST

This is a method that allows for continuous documentation of visible alterations and movements in laryngeal structures during all phases of the respiratory cycle, from rest to peak exercise and back at rest (Video #1 and # 2). The method is easy to perform and well tolerated from five years of age. In our diagnostic setup, synchronised cardiopulmonary exercise data and video recordings of the larynx, the upper part of the body and sound tracks are all merged into one digitalised file and stored for later review and analysis [30]. It has been argued that the CLE-test is too resource intensive, and that a laryngoscope held by the hand with the patient exercising on a bike will serve the same purpose. This may be so, but the laryngoscope should be in place throughout the complete exercise session; i.e. from *before* the onset of symptoms, through peak exercise and preferably until the symptoms resolve. The findings must be recorded for documentation and later assessment. Only then can important characteristics be revealed, documented and made communicable to others, such as which structures incited and perpetuated the abnormal laryngeal movements that gave rise to the symptoms.

WHAT MODE OF EXERCISE SHOULD BE USED TO REPRODUCE EIIS?

Treadmill running, ergometer cycling, rowing or stair climbing have all been used to reproduce EIIS in a diagnostic setting [20,30,38,41,44,45]. Ideally, the mode and the degree of exercise should be tailored to the individual patient, based on triggers identified from the medical history, nicely described in humans by Panchasara et al. [45] as well as in race horses by Strand et al. [46]. In a laboratory setting one must compromise, and as a minimum ensure that exercise continues to exhaustion or to intolerable symptoms. In most young people, treadmill exercise is better than exercising on a bicycle to achieve this aim [47] possibly exemplified by Tervonen et al [38]. They used a stationary bicycle and were unable to reproduce symptoms in 50% of patients with EIIS and made laryngeal findings in 30% [38].

WHAT ARE THE NORMAL LARYNGEAL RESPONSES TO EXERCISE?

During exercise, the larynx normally opens fully and the epiglottis rotates anteriorly towards the base of the tongue [41], stretching the aryepiglottic folds, thereby allowing for increased airflow with the least possible increase of airflow resistance (Video # 3) [40]. Several muscles are active in this process [48]. The motion of the arytenoids occurs in three dimensions i.e. sliding, tilting and rotation along the vertical axis. The top of each cartilage determines the position of the dorsal end of the aryepiglottic folds, whereas the anteriorly and caudally placed vocal processes

determine the positions of the dorsal end of the membranous part of each vocal fold. In the abducted position, the dorsal part of vocal folds is lifted cranially. Normally most of the airflow through larynx takes place in the dorsal part of the glottic aperture. The posterior cricoid muscle (PCA) is the only abductor of the glottis, acting synchronised with and ahead of the diaphragm [48–50].

A slight adduction of the aryepiglottic folds at maximum minute ventilation was observed in 40% of subjects without respiratory complaints participating in a study performed by our group [10] and was therefore considered a normal phenomenon [51]. Bent and co-workers made similar observations [41]. Regarding the vocal gap, McFadden et al. proposed that an adduction exceeding 50% was consistent with VCD [19]. These issues need to be addressed in larger studies. Particularly, we have no knowledge on what are normal or optimal relations between body size, ventilatory requirements and the size (absolute) of the laryngeal aperture. Thus, a similar extent of adduction is likely to have different consequences in a narrow compared to a wide larynx and also for a competing athlete compared to a sedentary person.

WHAT ARE THE TYPICAL FINDINGS IN PATIENTS WITH EIIS?

After having performed more than one thousand CLE-tests in patients with EIIS, we are unable to pinpoint one single causal factor, and we certainly do not approve of the alleged importance of the vocal folds. The anatomy, physiology, innervation and function of the larynx are complex matters, and corresponding heterogeneities regarding exercise induced malfunction therefore should be expected. In 151 patients with EIIS examined with CLE test, there was abnormal laryngeal function in 113 (75%) and the adduction started in supraglottic structures in 109; however, with secondary glottic involvement in 88 [10]. These are findings supported by others who have utilized continuous laryngoscopy as a diagnostic method [7,8,52,53]. Thus, in a majority of patients with EIIS, adduction of the vocal folds does not seem to be a primary event, but rather a consequence or an associated phenomenon secondary to supraglottic alterations. There are authors who argue that exercise induced VCD or “paradoxical vocal fold motion” (PVFM) may be diagnosed based on the presenting symptoms alone, and that laryngoscopy is difficult and even unnecessary [12]. This strongly contradicts the experience gathered by our group and by others; with EIIS being associated with a wide spectrum of structural and functional abnormalities [7,8,10,53,54].

These distinctions are certainly of practical importance, as patients with severe collapse of supraglottic structures can be cured by laser supraglottoplasty [55–58]. Moreover, this attitude will leave an unknown number of patients with EIIS caused by extra-laryngeal obstruction with no (or an incorrect) diagnosis, potentially delaying or even preventing correct treatment. Thus, the continued and uncritical use of phrases like VCD or PVFM in relation to exercise related breathing problems should finally come to an end [12,16].

WHAT MIGHT BE THE CAUSAL FACTORS LEADING TO E-ILO?

Given the aforementioned heterogeneity as regards laryngeal findings, a similar heterogeneity as regards causal factors seems plausible. None of the theories listed below have been substantiated by adequate research. Thus, there is a large gap in knowledge that needs to be filled.

a) Aerodynamic principles

The Bernoulli principle states that increasing airflow through a tube creates increasing negative pressures within the tube

[59]. Depending on airflow velocity, turbulence and the strength of the supporting structures, sooner or later the tube will yield to these forces. In the case of the laryngeal aperture, the flow-rate at which this will occur is determined by the area and configuration of the laryngeal opening, and the “internal laryngeal solidity”, and the external support from the surrounding structures. Thus, e-ILO may be explained by poor support from muscles, ligaments or the laryngeal cartilages.

A weakness of the PCA-muscle or of the structures that stabilise the arytenoids and keep them upright and laterally positioned, may reduce the size of the laryngeal aperture, possibly to below a critical level required for an advantageous aerodynamic inspiratory flow pattern [50,60]. A secondary medial motion of the vocal folds may thus be explained by an increased negative pressure in the space between the vocal folds, due to changes of airflow induced by medial movements of the structures above [60]. This sequence would fit the observations made by most participants in studies made by our group and those of others who have performed laryngoscopy continuously throughout exercise tests [7,8,10,30,38,52,53]. It has been speculated whether there is a connection between infantile laryngomalacia and subsequent e-ILO. There is some evidence for this view, but the number of observations are modest and more studies are needed [61,62].

b) Laryngeal hyper-reactivity and changes in reflex interaction

Neural reflex loops are important for adequate laryngeal function in relation to respiration, swallowing and protection against aspiration. The idea of “reflex associated VCD” is that direct stimulation of sensory nerve endings in the respiratory tract may induce protective reflexes, leading to laryngeal closure [63]. Mechanical or chemical stimulation of the supraglottic mucosa or direct stimulation of the superior laryngeal nerve may activate the laryngeal adductor reflex to protect the airway from aspiration or asphyxiation [64]. Exercise related hyperventilation could conceivably represent a trigger, with a variable sensitivity leading to a corresponding variability in the threshold for laryngeal closure in the general population. So far, we lack evidence to support this theory.

c) Laryngopharyngeal reflux

Gastroesophageal reflux has been associated with VCD by several authors [36,65]. The argument has been that acidic reflux reaching the laryngopharyngeal area should induce a hyper-excitable state [36,66]. If a causal relationship is present, one would expect that treatment with proton-pump inhibitors should reduce reflux symptoms as well as the EIIS. Maturro et al. reported three patients with VCD and laryngopharyngeal reflux treated with proton-pump inhibitors with a positive effect on the reflux but not on the VCD [12]. A recent study indicated that subjects with high reflux symptom-index in fact had reduced laryngeal sensitivity [67]. It is important to remember that the prevalence of reflux in unselected populations vary between 10% and 60% [68]. One should be careful proposing causal relationships that involve conditions with this kind of prevalence.

d) Psychological aspects and e-ILO

VCD tend to be interpreted within a psychological paradigm. In their review article, Leo & Konakanchi reported from a sample of 171 cases with “paradoxical vocal cord motion” (PVCM), and found that only 7% did not have a psychiatric diagnosis [15]. Others have claimed that VCD represents the physical manifestation of underlying psychological problems [14]. Sexual abuse in early

childhood is still being put forward, based on a small study from the 1990s [13].

In this context it is probably important to distinguish laryngeal obstruction occurring at rest from that induced by exercise. Based on two decades of personal experience working with children and adolescents with exercise-induced symptoms, we have found no reason to suspect that a majority of patients with EIS and e-ILO suffer from mental health problems. It is our impression that most are otherwise healthy and physically active young people who benefit from an explanation that their breathing problem is not dangerous, and that there is nothing mentally wrong with them. However, we have certainly observed that many patients are concerned and sometimes frightened by their symptoms, and therefore reluctant to expose themselves to situations they know will provoke them. In our opinion this reaction is understandable, considering the trauma of experiencing a 'blocked airway' during heavy exercise. The panic reactions observed in some should not be interpreted as a cause of their breathing problem, but rather as a response to the choking feeling of laryngeal collapse. If a laryngoscope is introduced in a panicking patient after the exercise has stopped, and without knowledge of what preceded this situation in the larynx, the image will simply reveal adducted vocal folds in a panicking patient, and therefore erroneously be interpreted as vocal fold adduction induced by hysteria.

Thus, post-exercise laryngoscopy entails a high risk of making the classical mistake of reverse causality; i.e. *panic does not cause e-ILO, but is caused by e-ILO*.

As this group of patients is characterised by its heterogeneity, we do not exclude that stress, anxiety and competitive personalities may worsen and possibly also trigger symptoms and findings, but argue that organic, structural problems make the e-ILO response possible in most patients. This point of view is strengthened by the convincing effect of surgical treatment in selected severe cases [55–58,69].

e) Environmental conditions and e-ILO

Temperature and humidity are involved in the pathogenesis of EIB [70,71]. Regarding EIS and e-ILO little is known. In our experience, participants in winter sports particularly, but also swimmers, handball, basket and soccer players seem to be over-represented. Most patients state that a cold climate reduces their tolerance to exercise. These findings correspond partly to the descriptions given by Rundell, reporting that inspiratory stridor was more prevalent in outdoor (8,3%) compared to indoor athletes (2,5%) [20]. Collectively, these observations indicate that environmental factors might be involved in the aetiology of e-ILO; however, the exact mechanisms remain unknown.

f) Age, gender and physical capacity in relation to e-ILO

EIS seems to start in early adolescence in the majority. The design of the aryepiglottic folds and the cuneiform tubercles make the supraglottic opening relatively narrower in adolescents than in adults and the epiglottis is longer and may be curved or omega-shaped [72,73]. Relative to body size, maximum oxygen uptake peaks in adolescence, and this must necessarily be reflected by the minute ventilation. Most agree that e-ILO is overrepresented in girls [7,8,10,28,74]. Anatomical studies have shown no gender differences in the relative size of the laryngeal aperture before puberty, while there are significant gender differences throughout the pubertal growth spurt [73,75]. These factors may all contribute to the age and gender distribution of e-ILO. Familial clustering of e-ILO does not seem uncommon in clinical practice; however, the role of heredity has not been established.

WHAT ARE THE TREATMENT OPTIONS FOR E-ILO?

Treatment of e-ILO can currently be seen as an evidence-free zone (Figure 3) and thus, all interventions must be planned in close cooperation with a well-informed patient and his/her caregivers within the frames of the principles of 'shared decision making' [76,77].

In most studies aiming to address treatment of e-ILO, inclusion was based on the symptoms presented by the patients. The same applied to outcome measures; i.e. in most studies inclusion as well as success rates were based on subjective patient reports. Moreover, in most studies patients with EIS were treated as if they were all suffering from one disease entity, often labelled exercise induced VCD. Few studies have based inclusion and treatment strategies on verifiable findings or created a targeted strategy to deal with this. Given the heterogeneity of laryngeal findings that has been reported in patients with relatively similar symptoms [7,8,10,39,52,53], it seems that conclusions from these studies should be interpreted very cautiously. Another complicating factor is the role played by placebo effects in studies utilizing open label designs and methods such as psychotherapy or speech therapy [12,19,22,25,28,35,78–81]. Inhaled ipratropium bromide applied locally prior to activity has been reported to prevent exercise induced VCD [82]. Different forms of biofeedback techniques have been proposed [83,84], as has inspiratory muscle training [85–88]. Laser supraglottoplasty has been used to treat patients with severe supraglottic e-ILO and positive effects have been reported by several research groups [41,52,54–58,69,89–91]. Selection of patients for surgical treatment should be performed with great care, and surgery should not be performed without prior laryngoscopic assessment performed continuously throughout a maximal exercises test, particularly avoiding surgery in patients with a primary glottic e-ILO [55,56,69]. Potential gains must be carefully weighed against the risk of potential complications. The complication rates and long-term effects need to be established. The place for surgery in the treatment of e-ILO has not yet been settled.

Video recorded verification of laryngeal obstruction may be of value not only as a diagnostic tool, but also as a therapeutic measure. Simply observing their own malfunctioning larynx directly on a film is of help in a majority of patients with mild or moderate disease. The recordings are also highly educational in the process of providing direct advice with real-time visual feedback to the patient as regards what is a rational breathing pattern during exercise, and how changes may influence the patency of the larynx. However, these are clinical observations made by our group during routine work, not substantiated scientifically.

In conclusion, randomised controlled trials are imperative in this field of respiratory medicine, with the inclusion to studies as well as the assessment of success performed using objective and verifiable measures.

WHAT IS THE PROGNOSIS OF E-ILO?

It has been suggested that laryngeal growth and maturation during puberty should make the larynx more resistant to inward collapse during high minute ventilation [92]. In a 2-5 year follow-up study, Maat et al. were unable to show that growth by itself could cure e-ILO [56]. Patients reported less symptoms but also lower levels of activity, suggesting changes to a lifestyle not challenged by laryngeal airflow limitations. Most patients reported that being assigned a diagnosis and to actually see what took place in their larynx was important for a perception of safety in relation to exercise and to maintain a reasonable level of physical activity. Among those with supraglottic obstruction who had been treated surgically, nearly all were cured [56].

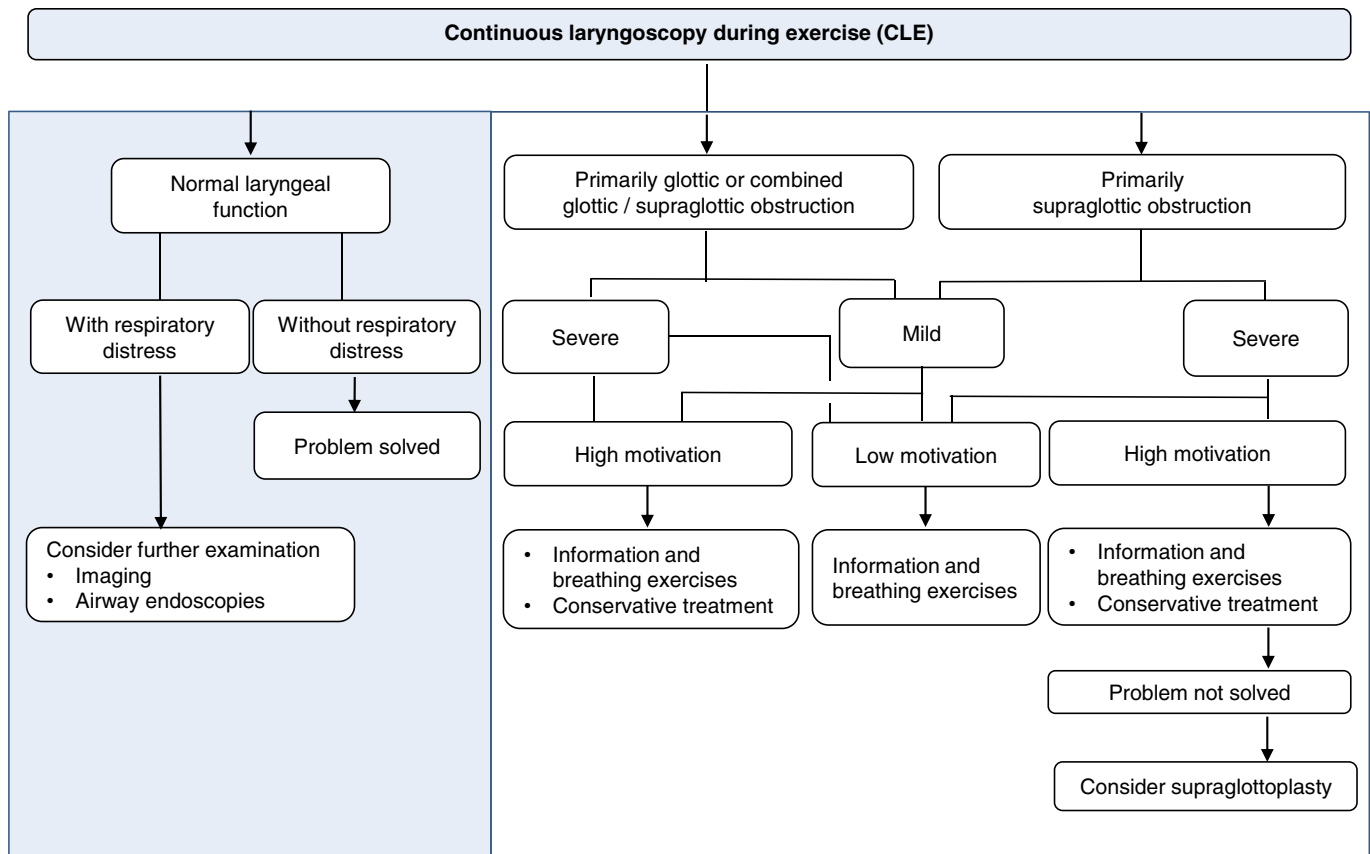


Figure 3. For simplicity, laryngeal findings are dichotomized in mild and severe, modified after Maat et al. [51]. Treatment of e-ILO is a virtually “evidence free zone”. Some suggested options involve long-lasting treatment efforts or are irreversible (surgery). Thus, treatment of e-ILO requires ‘shared decision making’ [77]. It is our experience that provision of information and advice, in addition to access to diagnostic films with the opportunity to practice biofeedback, is perceived as adequate in a large number of cases. Conservative treatment in our unit currently implies entering a structured program involving speech therapy and/or inspiratory muscle training, both lasting several months.

HOW SHOULD WE MANAGE E-ILO IN A CLINICAL SETTING?

Based on our clinical experience we have prepared a flow chart that describes how we currently treat our patients (Figure 3). Most of what we suggest has not been substantiated by proper scientific evidence, and more and better research is imperative. This situation also underlines the need for ‘shared decision making’ [77]. The precise nomenclature recently provided by the ERS/ELS/ACCP Task force group will facilitate future studies from which data can be pooled and outcomes compared.

POTENTIAL CONFLICT OF INTEREST

Haukeland University Hospital owns part of US patent no. 11/134551, protecting the commercial rights of the CLE test

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AUTHORS’ CONTRIBUTIONS

All authors made a significant contribution to the conception and the design of the article and of the collection, analysis and interpretation of the data, drafting of the article and revising it critically for content and final approval of the version to be published. All authors participate in the “Upper Airway Group” of

Haukeland University Hospital and are collectively responsible for the final version of this paper.

FUTURE RESEARCH DIRECTIONS

- Abnormal vs. normal and optimal laryngeal function during high intensity exercise.
- Understand the various subtypes of e-ILO.
- The role of psychological factors and mental disorders for e-ILO.
- Evidence based treatments, targeted to the various subtypes of e-ILO.

PRACTICE POINTS

- Upper airway obstruction can cause exercise induced inspiratory symptoms (EIS).
- EIS peaks during ongoing exercise and resolves rapidly when stopping.
- EIS is most often linked to inducible laryngeal obstructions (ILO), labelled e-ILO.
- E-ILO usually starts supraglottic and is followed by glottic involvement as the exercise load and ventilatory requirements increase.
- Laryngoscopic findings are important for correct treatment and further management.
- Most treatments for e-ILO are based on weak evidence.
- Most patients with e-ILO benefit from individualised information and guidance.

EDUCATIONAL ARTICLE

You can receive 1 CME credit by successfully answering these questions online.

- Visit the journal CME site at <http://www.prrjournal.com>.
- Complete the answers online, and receive your final score upon completion of the test.
- Should you successfully complete the test, you may download your accreditation certificate (subject to an administrative charge), accredited by the European Board for Accreditation in Pneumology.

SELF-EVALUATION QUESTIONS

- What would be a preferred approach to diagnostic workup in a patient presenting with EIBS?
 - Referral to a psychologist or a psychiatrist
 - Terminate high intensity physical activity
 - Methacholine bronchial provocation test
 - Test for exercise induced bronchoconstriction
 - Laryngoscopy during a maximal intensity exercise test
- Which of the following are typical of EIB?
 - Onset during heavy exercise
 - Onset after stopping heavy exercise
 - Response to short-acting β_2 -agonist
 - Difficulty breathing out
 - Difficulty breathing in
- Which of the following are typical of e-ILO?
 - Onset during heavy exercise
 - Onset after stopping heavy exercise
 - Response to a short-acting β_2 -agonist
 - Difficulty breathing out
 - Difficulty breathing in
- What could be a preferred management of a patient with documented e-ILO?
 - Terminate all sorts of physical activity
 - Bio-feedback
 - Ipratropium bromide
 - Short-acting β_2 -agonist
 - Antidepressive medication
 - Treatment with breathing techniques
- Which organ structure(s) is (are) most often primarily involved in e-ILO?
 - It is primarily a psychological problem
 - The lungs
 - The vocal cords
 - The cardiovascular system
 - None of the above

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.prrv.2016.07.003](https://doi.org/10.1016/j.prrv.2016.07.003).

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