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Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement

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ABSTRACT Inducible laryngeal obstruction (ILO) describes an inappropriate, transient, reversible narrowing of the larynx in response to external triggers. ILO is an important cause of a variety of respiratory symptoms and can mimic asthma. Current understanding of ILO has been hampered by imprecise nomenclature and variable approaches to assessment and management. A task force of the European Respiratory Society (ERS) and European Laryngological Society (ELS) was thus set up to address this, and to identify research priorities.

A literature search identified relevant articles published until June 2016, using all identifiable terms for ILO, although including only articles using laryngoscopy. In total, 172 out of 252 articles met the inclusion criteria, summarised in sections on diagnostic approach, aetiology, comorbidities, epidemiology and treatment. The consensus taxonomy published by ERS, ELS and the American College of Chest Physicians (ACCP) in 2015 is used throughout this statement.

We highlight the high prevalence of ILO and the clinical impact for those affected. Despite recent advances, most aspects of this condition unfortunately remain incompletely understood, precluding firm guidance. Specifically, validated diagnostic and treatment algorithms are yet to be established, and no randomised control studies were identified in this search; hence we also make recommendations for future research.

Introduction

A seminal report was published in the *New England Journal of Medicine* in 1983, describing the characteristics of five patients who presented with unexplained dyspnoea and wheeze [1]. Although they mimicked asthma, these clinical features arose from inappropriate or "paradoxical" laryngeal closure. This description of vocal cord dysfunction (VCD) highlighted the importance of functional laryngeal obstruction (*i.e.* without apparent structural or neurological cause) as a distinct clinical entity. The authors proposed that the disorder was likely to "be more common than originally thought and may be part of a spectrum of breathing disorders related to abnormalities of the larynx".

Since that time, our understanding of disorders associated with paroxysmal laryngeal closure has evolved, and there are currently a large number of published reports describing the epidemiology, aetiology, clinical characteristics and treatment options. Moreover, technical advances have enabled dynamic endoscopic assessment of the upper airway. As a result, there is a growing understanding of the variety of phenotypes that might lead to laryngeal closure [2] and a growing awareness of the high prevalence of laryngeal closure causing exertional breathing problems in otherwise healthy young individuals [3].

In response to this evolving evidence base, a task force for inducible laryngeal obstruction (ILO) was established in 2010, including paediatricians, pulmonologists and otorhinolaryngologists with specific expertise in this field. The task force had two key aims: 1) to provide and establish an internationally accepted consensus nomenclature to describe paroxysmal and episodic laryngeal closure and 2) to evaluate the literature in the field; in order to identify important deficits in our current clinical knowledge base and thus direct future research priorities.

The first aim was achieved with collaboration between the European Respiratory Society (ERS), the European Laryngological Society (ELS) and the American College of Chest Physicians (ACCP) at the ERS/ELS/ACCP 2013 International Consensus Conference. The term ILO was accepted and defined as inducible (*i.e.* by an external stimulus) laryngeal obstruction causing breathing problems; this term will be used throughout this article [4].

This article, authored by the current ERS and ELS task force panel members, describes work addressing the second aim: detailing the findings of a systematic literature search, to present a state-of-the-art review on ILO. A key aim of this task force document is to use this appraisal process to make recommendations for future research, with the ultimate aim of facilitating and directing successful ongoing expansion of scientific knowledge in the field.

Methodology

Relevant articles published before July 2016 were identified by systematic searches in the Medline database (accessed through PubMed) and the Cochrane Database of Systematic Reviews. All possible terms for ILO known to the task force members were used in searches (a full list of search terms is presented in the online supplementary material). Additionally, reference lists from all articles where the subject of the publication fulfilled the ILO definition were further examined, and previously unidentified relevant publications were included. Only papers in English were selected, allowing all task force members to evaluate them. All original studies, cases, letters or other articles presenting new data with content matching the applied definition of ILO were included for further evaluation. The methodology for article selection is illustrated in figure 1.

We excluded reports in which the diagnosis of ILO was based solely upon symptoms or clinical features of laryngeal obstruction. Thus, the current review only includes reports describing objectively verified laryngeal obstruction, *i.e.* by fibre-optic laryngoscopy or imaging.

We classified the articles into expert opinion, case reports/case series, cohort studies, case–control studies or randomised clinical trials.

Electronic copies of all identified articles were made available to all members of the task force group. The entire manuscript was drafted and amended until supported unanimously by all task force members.
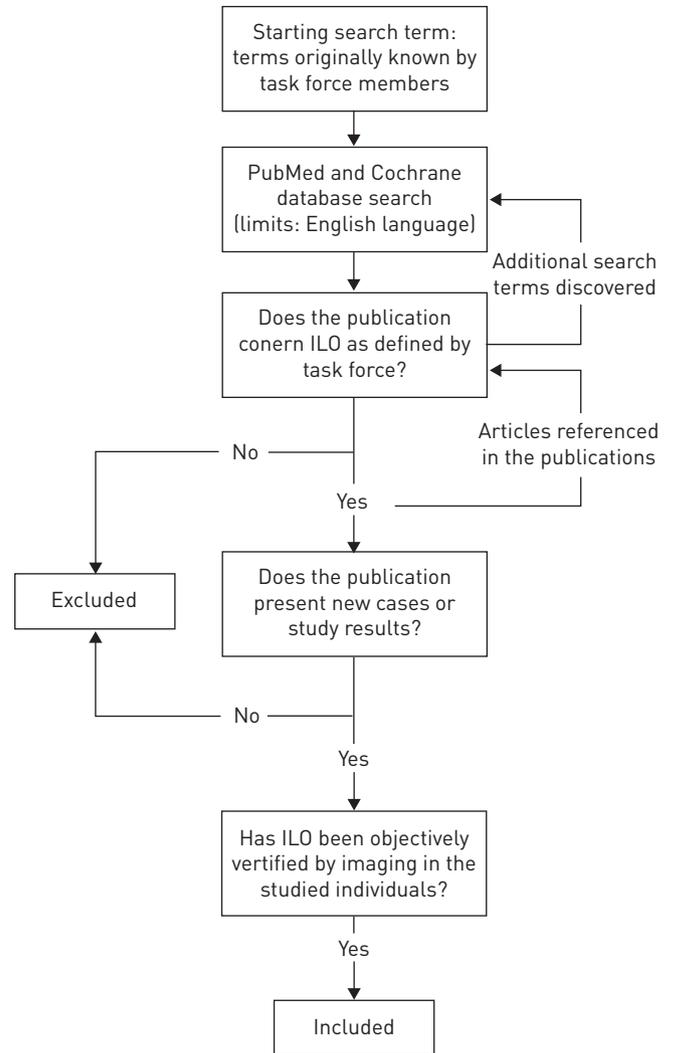
FIGURE 1 Search methodology. ILO: inducible laryngeal obstruction.

The primary search identified 252 articles for further examination. 172 articles matched the definition of ILO. Summary statistics of all matching articles can be found in table 1. The majority were classified as case reports or case series (n=136), cohort studies (n=25) or case–control studies (n=11). No randomised controlled trials or expert opinion studies were identified.

Diagnostic approach

Clinical features

A secure diagnosis of ILO is dependent on the presence of compatible clinical features, precipitated by exposure to an inducer or trigger and with concurrent objective verification of laryngeal obstruction, ideally by direct laryngoscopic examination [4].

Typical clinical features include wheeze, dyspnoea and cough, and these symptoms are highly variable and evanescent. In most cases, individuals with ILO will exhibit inspiratory breathing difficulties, although a pure expiratory form of ILO has been described [5].

When exercise is the inducer, the timing of symptom onset is informative. Symptoms of exercise-induced laryngeal obstruction (EILO) are typically maximal during strenuous exercise, in contrast to exercise-induced bronchoconstriction, in which symptoms typically can peak up to 20 min after exercise cessation. Dyspnoea caused by EILO can be accompanied by coarse or high-pitched inspiratory breath sounds, sometimes progressing to clear-cut stridor, and may be associated with severe respiratory distress, hyperpnoea and/or panic reactions, evolving in parallel with increasing ventilatory requirements throughout the exercise session. The term exercise-induced inspiratory symptoms has been introduced [2]; however, patients suffering from EILO are sometimes unable to attribute respiratory symptoms to a

TABLE 1 Summary of included articles

	Studies	Patients		
		Mean	Median	Total
Case report or case series	136	6	1	868
Case–control	11	75	97	826
Cross-sectional	25	59	60	1480
Total	172	18	1	3174

Data are presented as n.

specific phase of the breathing cycle, particularly when interviewed at a first consultation. Several studies indicate that self-reported symptoms are poor predictors of EILO [3, 6, 7].

There are several symptom questionnaires that attempt to detect ILO [8–10]. These focus on the glottic component of ILO, with the exception of the dyspnoea index [9], and have yet to be comprehensively validated in a multicentre context. However, questionnaires show promise as diagnostic screening tools, while providing a structured description of symptoms.

Laryngoscopic technique

We have described previously how to perform a laryngoscopic examination and standards with regard to the key findings that should be reported in all cases [4]. Specifically, the change in laryngeal features from baseline to the point of maximal obstruction should be described. Furthermore, whether the obstruction to airflow is at a glottic or supraglottic level should be detailed [3, 6, 11–13]. In cases of combined supraglottic and glottic involvement, the two levels of obstruction may not be co-temporal throughout the attack. For multilevel obstruction, the sequence of events should be described if possible. It is helpful to record the laryngeal movement continuously for later analysis.

The degree of laryngeal obstruction can vary from mild to severe [12], with near-complete closure in some cases [1]. There is currently no gold-standard validated scoring system that differentiates normal from abnormal responses. Proposed methods for image quantification of the degree of obstruction have included measurement of laryngeal anterior–posterior (A–P) diameter [14–16] and measurement of anterior glottic angle [15]. Continuous recordings have used subjective reviewer grading estimates of obstruction [12] and computerised calculations relative to measured change in the glottic or supraglottic aperture [17].

Some authors have hypothesised that introducing a laryngoscope into the nasopharyngeal space and/or applying local anaesthetics to the nasal cavity may affect laryngeal reflexes and thus confound the results. Research is needed to address this issue, but there is currently no published evidence to support this notion.

Inducers of laryngeal obstruction

The most common inducers of laryngeal obstruction are exercise, irritants and emotional stress. An inducer in this context is defined by its ability to trigger sufficient narrowing of the laryngeal space to cause breathing difficulties and a laryngoscopic image compatible with laryngeal obstruction to airflow. The task force acknowledges that to a large extent, the latter is subjective. Therefore, while awaiting objective assessment of this feature (*e.g.* accurate measurements, validated scoring systems or pressure change measurements) the method by which this assessment was performed should be detailed.

Exercise

Where exercise is an inducer, laboratory provocation studies attempt to simulate the real-life (*i.e.* in the field) scenario, but most commonly employ an indoor treadmill [11, 17, 18], stationary bicycle [19] or, very occasionally, other exercise modalities [20].

Exercise protocols vary, but all aim to exercise subjects until symptoms are elicited and/or peak exercise capacity has been achieved. EILO typically occurs at high levels of ventilation [13], which entails that a maximal exercise test protocol must be employed. These simulation methods have been applied in large studies of symptomatic individuals and in symptom-negative controls [2, 3, 6, 21], but their between-test reliability and validity remain to be established. Crucial in this context is the ability of the test set-up to facilitate sustained maximal efforts (beyond the aerobic threshold) for as long as necessary to induce
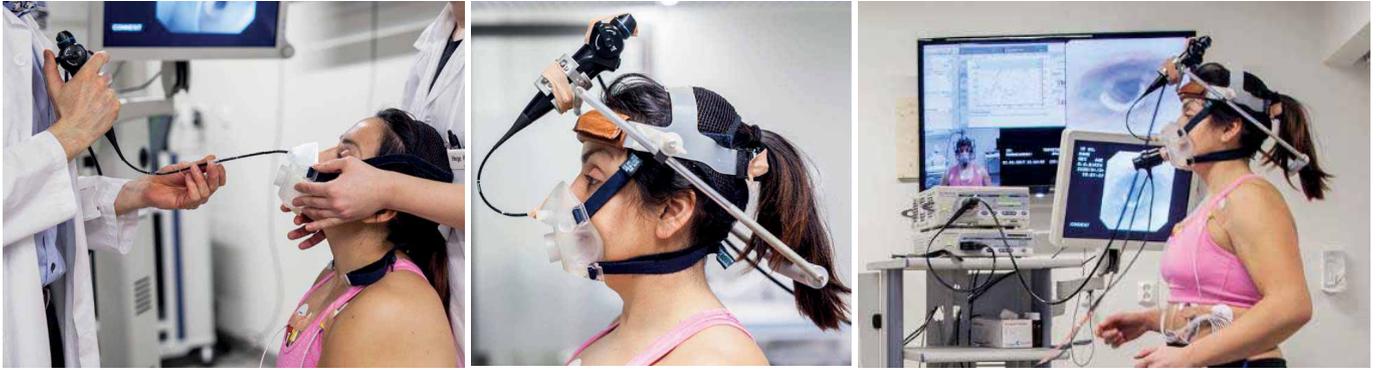
FIGURE 2 Continuous laryngoscopy during exercise. The laryngoscope is secured to a headset *via* a facemask. The screen shows real-time images of the patient, her larynx and cardiopulmonary exercise data while running.

symptoms. This might be more easily achieved if using free running or other 'in the field' techniques, as has been addressed in studies of exercise induced asthma [22]; however, this scenario has not been studied in relation to EILO.

The continuous laryngoscopy during exercise (CLE) test uses a flexible nasolaryngoscope fixed to a head apparatus, allowing real-time visualisation of the larynx throughout the study (figure 2) [11]. The CLE test has now been used in multiple research studies and provides recorded images detailing the temporal change of laryngeal obstruction, as it occurs during exercise [13]. The CLE test has helped establish the fact that EILO commonly arises from supraglottic (*i.e.* aryepiglottic fold) obstruction; however, in some cases it may be a pure glottic (*i.e.* vocal cord) phenomenon, or both can occur [2]. The relationship between laboratory EILO and EILO "in the field" is yet to be studied, and anecdotally, many athletes report heightened symptoms in the competitive environment (*e.g.* potential anxiety and physicality of competitive sporting events).

Irritants

A retrospective review included the first description of "irritant"-associated vocal cord dysfunction [23]. A variety of breathing and other problems were temporally associated with a single occupational (n=10) or environmental (n=1) exposure, based upon history alone, with no environmental exposure analysis. Inclusion required the patient's perception of a "gas smoke, fume, vapour, mist or dust". In several cases "…the exact offending agent(s) could not be determined…" nor was a physical "irritant" or injury effect documented, yet there was a presumptive attribution to "irritant inhalational injury". A broad range of irritants have been described in case reports and case series, including odours [10, 24, 25], sleep [26], stress [10], cold air [10], gastrolaryngeal reflux [27], environmental and occupational exposures [28–30], wood dust [31] and chemicals [29, 32, 33]. The causal mechanism of irritant ILO is unknown. It is unclear if irritant ILO is a direct response to the irritant stimulus itself, *e.g. via* mucosal inflammatory reactions, or related to altered reflex sensitivity, and to what extent psychological factors contribute; highlighting the lack of evidence in the field.

Use of surrogate inducers

Substitute (surrogate) methods for the inducer have been used to precipitate ILO. Specifically, the use of methacholine [7, 34], mannitol [7] and histamine [14, 35, 36] as laryngeal provocation agents has been studied, using standard bronchoprovocation test methodologies, but with a focus on the inspiratory component of the flow–volume loop on spirometric measurements.

The relationship between bronchoprovocation testing and ILO is complex and incompletely understood. Indeed, patients with laryngoscopic evidence of ILO may have ILO during methacholine challenge, as well as with saline placebo [37]. Many authors have concluded that methacholine challenge is of little help in differentiating EILO from asthma, and indeed, the two conditions may coexist [37–40]. In addition, it remains unclear whether substitute inducers and self-induction are comparable to the laryngeal response during a typical "symptomatic" episode.

Eucapnic voluntary hyperpnoea has been used with direct laryngoscopic visualisation [41], and can induce glottic as well as supraglottic obstruction. However, the sensitivity and specificity of these findings remain unclear, and in one study the authors commented that poor visualisation of the larynx limited the utility of this technique [41].

Use of surrogate means to detect laryngeal obstruction

Diagnostic methods other than laryngoscopy have been evaluated in the diagnosis of ILO; most often full flow–volume measurement with spirometry. Patients with ILO [1] typically have a normal flow–volume loop while asymptomatic; however, during a spontaneous episode a variable extrathoracic obstruction pattern can be present, *i.e.* with attenuation in the inspiratory flow compared to expiratory flow [1, 5, 39, 40, 42–44]. There are several causes of a blunted or truncated inspiratory flow–volume curve, including inadequate instruction, suboptimal effort or inability to perform the procedure, as well as other diseases such as diaphragm weakness, fixed large airway obstruction and any cause of reduced lung compliance [37]. It is therefore not surprising that the diagnostic precision of spirometric assessment of ILO is poor [39, 43]. One study evaluated the flow–volume loop before and after exercise, and found no correlation with laryngoscopy-documented ILO. The authors concluded that exercise-induced laryngeal obstruction cannot be diagnosed or excluded by physician-evaluated pre- and post-exercise flow–volume loops [45]. Similarly, assessment of intra-exercise tidal flow–volume relationships has not been systematically validated in a context of EILO diagnostics, presently precluding evidence-based use of these measures. Finally, flow–volume loops cannot differentiate supraglottic from glottic ILO, distinctions that have a bearing on choice of treatment. Thus, the use of flow–volume loops (resting and intra-exercise) as diagnostic tool in ILO needs to be further explored in future studies.

Forced oscillation techniques may be a diagnostic or screening tool for ILO [46–49]; however, the sensitivity and specificity of these methods are insufficiently described and more research is needed.

Computed tomography, with three-dimensional images of laryngeal obstructions, has been reported to identify ILO in a cohort of patients with difficult-to-treat asthma [50]. Limitations of this technique include the absence of documentation of a symptomatic spontaneous or provoked episode during testing, need for supine positioning and brief data acquisition window, due to concerns about radiation exposure.

Epidemiology

The reported epidemiology of ILO varies considerably, depending on the diagnostic criteria employed (table 2). Moreover, the literature is replete with case reports and small case series highlighting a number of questionable associations, for example a high prevalence of psychiatric comorbidity [1], some of which may be examples of Berkson's fallacy. Moreover, although clinical cohort studies of patients with ILO have now been published (table 2), any given cohort will be heavily influenced by referral bias and the perspectives of the authors, varying between psychiatric departments [51], paediatric departments [2], highly specialised otorhinolaryngology clinics [52], military institutions [43] and sports medicine settings [6, 40].

Key epidemiological data, such as prevalence, incidence, age and sex distribution of ILO are unknown in the general population. NEWMAN *et al.* [5] described 95 adults (84% female) hospitalised with laryngeal symptoms, with an average age of 39 years. In an evaluation of 1025 patients with dyspnoea, prescreening identified 63 potential patients of whom 29 (2.8%) were diagnosed with ILO [53]. When classified according to the original nomenclature of VCD in a 2010 review (n=1161), there was an approximately 2:1 female predominance, 71% were adults and the remaining 29% were predominantly adolescents [54].

The prevalence of EILO in adolescents and young adults appears to be in the range of 5–7% in northern Europe [3, 21]. Some, but not all studies report a higher female prevalence, discrepancies possibly related to the age of the subjects at assessment in the various studies. Thus, in a study of 94 patients diagnosed using the CLE test, average age was ~15 years, and 68% were female [55], similar to other adolescent groups (table 2). Exercise appears to be a more common inducer of ILO in younger age groups; however, this might be a biased impression based on different exercise habits in the different phases of life.

Details on presumed "irritant" ILO are limited, as irritant exposure is a less frequently reported inducer than exercise. In 11 cases of irritant-associated VCD, 73% were female and of a similar age (45 years) to a nonirritant-exposed VCD control group (n=33) with a 94% female predominance [23]. Evaluation of spirometry from workers at the World Trade Center disaster identified a cohort with possible irritant-induced VCD. From a sample of 172 individuals, 18.6% had variable extrathoracic obstruction and 10 (5.8%) patients were diagnosed with VCD [30].

Aetiology/pathophysiology

The human larynx has a number of highly complex functions; it must close to protect the airway from life-threatening aspiration, but must open fully during exercise in order to optimise airflow and thus exercise performance. Finally, it performs fine movements during phonation. Given these sophisticated roles it seems unlikely that a single factor could explain the entire range of manifestations of ILO.

TABLE 2 Key studies detailing the epidemiology of inducible laryngeal obstruction (ILO)

Authors [reference]	Year	Population	Design	Findings	Comments
HIRA and SINGH [46]	2009	n=51 Patients referred to tertiary centre for treatment-refractory asthma	Cross-sectional	24% had VCD Age 32.9±12.4 years 58% female IOS-positive in 58% of cases and 15% of controls	Only considers glottic ILO diagnosed at rest
RØKSUND et al. [2]	2009	n=151 cases and n=20 controls Patients with exertional dyspnoea consecutively referred to a tertiary clinic	Cross-sectional	75% had EILO Age 16.3±7.3 years 72% female Detailed description of laryngoscopic presentations	Highly selected population
CHRISTENSEN et al. [21]	2011	n=98 (n=556 invited to participate) General population	Cross-sectional	43% had EILO Age 19 (14–24) years Female/male odds ratio of having EILO was 3.41 79% supraglottic, 14% glottic, 7% mixed glottic and supraglottic 70% had verified airway hyperresponsiveness to methacholine Estimated prevalence of EILO in the general population: 7.6%	Selection bias from 2-day work-up
NIELSEN et al. [6]	2013	n=88 Athletes referred to CLE in a tertiary asthma clinic	Case series	35% had EILO Median (IQR) age 18 (11) years 77% female 43% had verified asthma	Retrospective design Highly selected population
TILLES et al. [103]	2013	n=143 Patients with EILO confirmed by post-exercise laryngoscopy	Case series	All EILO-positive (by design) n=83 glottic (84% female); age 14±2.6 years n=60 supraglottic (77% female); age 14±2.3 years	Retrospective design Highly selected population Post-exercise laryngoscopy
MARCINOW et al. [104]	2014	n=46 Elite athletes and age- and sex-matched non-athletes, both with verified PVFMD	Case–control	All PVFMD-positive (by design) Age 21 (18–69) years 70% female 39% had verified asthma	Retrospective design Highly selected population Only glottic component considered
HANKS et al. [105]	2012	n=148 Athletes referred to a tertiary asthma clinic for evaluation of exertional dyspnoea	Cross-sectional	70% of tested (n=82) had VCD Median age 19 years 73% female 31% of VCD-positive subjects had verified EIB 6% had verified asthma	Retrospective design Diagnosis by videolaryngostroboscopy
JOHANSSON et al. [3]	2015	n=125 (n=2309 screened) General population with exertional dyspnoea	Cross-sectional	11% of cases and 4% of controls had EILO Mean (range) age 14.2 (13–15) years Estimated prevalence of EILO in the general population: 5.7% (equal for male and female) 44% of EILO-positive subjects had verified EIB	Well-designed Did not report details on glottic/supraglottic components

TABLE 2 Continued

Authors [reference]	Year	Population	Design	Findings	Comments
HILLAND et al. [58]	2016	n=20 (cases) Patients with a history of childhood laryngomalacia requiring hospital admission	Case–control	70% EILO-positive Age 12.7±2.7 years 35% female 70% supraglottic 45% of EILO-positive subjects had anomalies at rest	Highly selected population
WALSTED et al. [7]	2016	n=37 Patients with suspected asthma and exertional dyspnoea referred to a tertiary asthma clinic	Cross-sectional	22% EILO-positive Median (IQR) age 22.5 (12) years 100% female 88% supraglottic 14% of EILO-positive had verified asthma Inspiratory flow in mannitol and methacholine tests were poor predictors of EILO	Selected population

Data are presented as mean±SD or median (range), unless otherwise stated. VCD: vocal cord dysfunction; IOS: impulse oscillometry; EILO: exercise-induced laryngeal obstruction; CLE: continuous laryngoscopy during exercise; IQR: interquartile range; PVFMD: paradoxical vocal fold motion disorder; EIB: exercise-induced bronchoconstriction.

Mechanical insufficiency

It is likely that mechanical factors, based upon pressure change across the laryngeal inlet, are relevant in ILO triggered by exercise. The Bernoulli principle states that increasing airflow through a tube creates increasing negative pressures within that tube [56]. For the laryngeal aperture, the flow rate at which this will occur is determined by the area and configuration of the laryngeal opening and external support from surrounding structures. Thus, EILO may be explained by laxity of muscles, ligaments or the laryngeal cartilages. Of possible interest in this context is a relationship between congenital laryngomalacia (CLM) and EILO as proposed by SMITH et al. [57] in 1995, and a link from CLM to adolescent EILO proposed in a small study by HILLAND et al. [58] in 2016. Certainly, there are no studies to date that indicate that EILO in general can be explained simply by CLM; however, these two studies underline that laryngeal structure does seem to be relevant for EILO and that a history of CLM may be of relevance in some subgroups.

The posterior cricoarytenoid (PCA) muscle is the principal laryngeal abductor. Thus, a malfunctioning PCA muscle may lead to a smaller laryngeal aperture, possibly to a size below a critical level during high airflow states (i.e. exercise) [59].

The presentation of EILO is most frequently described in early adolescence and more often in females [2, 3, 21, 37]. The aryepiglottic folds and the cuneiform tubercles make the supraglottic opening relatively narrower in adolescents than in adults [60, 61]. There is no sex difference in the relative size of the prepubertal laryngeal aperture, while significant sex differences are described to occur throughout the pubertal growth spurt [61, 62]. These factors may all contribute to the age and sex distribution of the EILO epidemiology. However, changes with time and growth or differences as regards exercise habits, symptom awareness or other factors could also be involved and this needs to be explored in studies.

Neural dysfunction

Neural reflex control is important for adequate laryngeal function in relation to respiration, swallowing and protection against aspiration. The hypothesis behind reflex-associated VCD is that direct stimulation of sensory nerve endings in the respiratory tract may induce a protective reflex, triggering laryngeal closure [23]. 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 [63].

As discussed in detail below, gastro-oesophageal reflux (GOR; both acidic and nonacidic) may sensitise the glottal closure reflex [34, 64]. However, paradoxically, evaluating laryngeal sensitivity with direct mechanical stimulation has indicated reduced laryngeal sensitivity in the presence of reflux [65]. This may explain anecdotal reports of proton-pump inhibitors improving reflux, but not VCD [52]. Furthermore,

and again anecdotally, a cold climate reduces exercise tolerance in patients with EILO, and inspiratory stridor is more prevalent in outdoor (8.3%) compared to indoor athletes (2.5%) [40]. Collectively, these observations indicate that environmental factors might be involved in the aetiology of EILO; however, mechanisms remain unknown and should be addressed in future studies.

Psychological contribution

Several studies indicate the importance of considering a psychological contribution in ILO [51, 66, 67]. Specifically, in a sample of 171 cases with paradoxical vocal cord motion, only 7% did not have a psychiatric diagnosis [51]. Others have claimed that VCD represents the physical manifestation of underlying psychological problems [68]. These statements have been disputed, with the authors arguing that the tendency for panic observed in some patients is caused by the choking feeling of laryngeal collapse during heavy exercise, rather than being the cause of EILO [2]. These complex issues need to be addressed in properly designed studies.

Comorbidities

Several comorbidities may contribute to ILO, including asthma, GOR disease and nasal disease (*e.g.* sinusitis).

Asthma

ILO has long been recognised to mimic asthma [1], but is increasingly recognised to coexist with asthma. The contribution of each to a given episode of respiratory distress may be difficult to determine.

The use of standard effort-dependent lung function methods for diagnosis of comorbid asthma requires reliable, consistent and reproducible results. However, patients with ILO have been reported to have difficulty performing reproducible maximal flow–volume loops [29, 33]. If the vital capacity is reduced due to inducible laryngeal inspiratory obstruction, the forced expiratory volume in 1 s (FEV_1) is also likely to be reduced, potentially leading to an erroneous diagnosis of asthma, although the FEV_1/forced vital capacity ratio may be normal and suggestive of a restrictive, not an obstructive, pattern. The flow–volume loop in a symptomatic patient with confirmed inspiratory and expiratory ILO, and unequivocally excluded asthma, can still demonstrate a concave reduction in expiratory flow, mimicking asthma. Moreover, if only the percentage reduction in FEV_1 data is reviewed in interpretation of bronchoprovocation studies, such as a methacholine challenge, a misdiagnosis of asthma can be made.

Bronchoconstriction may itself induce laryngeal obstruction, which presents a significant barrier to the robust scientific study of asthma as a comorbidity of ILO. Use of endoscopic photography in normal subjects [14] demonstrated true vocal fold adduction on inspiration and expiration with reduced glottic area during histamine-induced bronchoconstriction measured with spirometry. Thereafter, 34 patients with obstructive lung disease of varying severity on spirometry were examined using endoscopic photography and calculation of glottic area referenced to a separately established constant A–P glottis diameter [69]. Results showed that glottic area (due to adduction of the true vocal folds) decreased proportionally to the decrease in FEV_1 on inspiration and expiration, and was more pronounced on expiration.

Future investigations should utilise objective diagnostic methodology to explore the possible associations between ILO and asthma, and to elaborate on these rather old studies. However, two important practical points can be extracted from the available literature: every effort should be made to diagnose asthma objectively [70], and secondly; in known asthmatics, it should not be assumed that all episodes of respiratory distress are due to asthma.

Reflux

Objective studies using manometry or impedance in patients with documented ILO have not been conducted to confirm that GOR episodes occur in a temporal relationship to symptomatic ILO episodes [71]. Patients with documented GOR and cough had significantly reduced laryngopharyngeal sensitivity, defined as the lowest air pressure required to induce the laryngeal adductor reflex, a transient episode of true vocal cord adduction. In short, the laryngeal adductor reflex threshold was higher in the GOR group. Laryngopharyngeal sensitivity was then compared before and after laryngopharyngeal infusions of normal saline and 0.1 N hydrogen chloride on separate days. In normal subjects the laryngopharyngeal sensitivity threshold for the laryngeal adductor reflex was significantly raised with acid, but not saline infusion, suggesting that small amounts of acid infusion into the laryngopharynx significantly impaired sensory integrity. A follow-up study [72] confirmed that the laryngopharyngeal sensitivity threshold for the laryngeal adductor reflex was elevated in GOR. Nonetheless, a smaller volume of infusion directly into the laryngopharynx was required to trigger the laryngeal adductor reflex in patients with GOR than in normal controls.

Nasal disease

Sinus computed tomography in patients with laryngoscopy-confirmed ILO was compared to patients presenting to the emergency room with acute asthma, patients with nonacute asthma and nonasthmatic controls [73]. There was extensive sinusitis in 23 of 74 acute asthmatics, five of 29 nonacute asthmatics, two of 59 controls and none of 13 ILO patients. The authors concluded that patients with ILO could be distinguished from asthma by sinus computed tomography, but the evidence is inconclusive, and in any event, the two frequently coexist.

Treatment

General approach

There are currently no published randomised controlled treatment trials. Even anecdotal reports frequently do not adequately confirm the diagnostic work-up and the outcome measure(s) that were applied, or characterise the type or severity of ILO. Multiple and often vaguely described management steps and a multitude of anecdotal reports complicate an overall interpretation. There is thus an urgent need for systematic and focused randomised controlled trials, with inclusion criteria as well as outcome assessment performed objectively. 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 has been reported to be of help in a majority of patients with mild or moderate disease [55]. Furthermore, simply identifying the problem may prevent inappropriate escalation of asthma therapy [74].

Medical treatment

Removal of irritants

GOR may be a trigger for ILO, and thus antireflux therapy has been reported to be efficacious by some [75], but not all [27, 52] authors.

Speech therapy/physiotherapy/psychology support

Speech therapy ILO treatments have applied various techniques with different reported outcomes [1, 39, 43, 52, 76–80]. Examples are nasal breathing, panting and diaphragmatic breathing [1, 76, 81]. Any method, such as speech therapy, that focuses attention away from the larynx (*e.g.* nasal breathing, diaphragmatic breathing) may have an effect through distracting the attention away from breathing problems and refocusing attention to a specific task (*e.g.* exercise).

Psychological mechanisms may have wide implications for various presentations of ILO. Several authors have reported successful treatment of ILO by psychotherapy [1, 82]). There is limited experience with hypnotherapy [83, 84] and biofeedback [39, 85, 86]. Psychotherapy or psychological counselling is often accompanied by speech therapy [1, 79, 87], and described with biofeedback [85].

Generally, a number of treatment strategies are aimed at avoidance of exposure to presumed inducers or represent methods for improved coping, including psychotherapy or psychological counselling, behavioural modifications and distraction techniques, including breathing techniques focusing attention away from the larynx. There is certainly a need to standardise these techniques.

Medicinal therapies

Inhaled anticholinergics (ipratropium) have been reported to reduce symptoms in exercise-induced VCD [88]. Properly conducted randomised controlled trials are needed.

Successful use of low-dose tricyclic antidepressants (amitriptyline) for night sedation was described in a group of 62 patients (age 18–90 years) in conjunction with a broad therapeutic approach, including speech and language therapy and in many cases the additional use of selective serotonin reuptake inhibitors. The authors called for randomised controlled trials before conclusions can be drawn [89].

Inspiratory muscle training

Case reports describe the application of inspiratory muscle strength training. It is speculated that laryngeal muscle strength is increased, possibly increasing the size of the inspiratory laryngeal aperture, as well as increasing respiratory muscle strength [90, 91]. However, an increase in laryngeal muscle strength has not been demonstrated. A potential concern is that enhancing the ability of the diaphragm and inspiratory accessory muscles to generate increased flow might be counterproductive if the larynx remains the critical restriction of ventilatory capacity. SANDNES *et al.* [92] showed that inspiratory muscle training did in fact produce laryngeal abduction in a healthy population.

Heliox

Heliox has been shown to relieve symptoms during an ILO episode and symptoms may remain resolved following gas withdrawal [1], possibly by reducing the work of breathing. A placebo effect cannot be excluded, as with so many interventions. Moreover, this treatment modality is impractical for most episodes of ILO.

Botulinum toxin injection

Experience in the treatment of ILO with botulinum toxin injections in the vocal folds is limited [86, 93–95]. In most cases, the treatment has led to resolution of the immediate symptoms, yet in some only with a transient effect, and in one case no effect at all [95]. From this paucity of evidence, it is not possible to determine the safety and efficacy of botulinum toxin injections. In addition, the indications for its use remain unclear and further studies are needed to determine the role of botulinum toxin injections as treatment for ILO.

Surgical treatment
Supraglottoplasty

Based on the finding that supraglottic ILO during exercise shows similarities to laryngomalacia in infants [57], several ENT surgeons have performed supraglottic surgery in patients with severe EILO and clinically significant breathing problems [55, 57, 96–100]. Collectively, <100 patients have been described, and all studies report benefit. The aim of the surgery has been to lower the height of the aryepiglottic fold in order to widen the laryngeal inlet and reduce laryngeal obstruction, thereby increasing exercise ventilatory capacity. These procedures resemble those performed in children with laryngomalacia, and have so far been performed in patients with supraglottic EILO without reports of serious complications [55, 98, 99]. By nature, supraglottoplasty is a treatment for supraglottic EILO (*i.e.* not for glottic forms of EILO); therefore underpinning the importance of CLE testing to establish the structural anatomical cause underlying each case of EILO [55]. To date, no randomised controlled trials of surgical treatment have been performed and indeed neither the optimal surgical technique nor the long-term outcome has been established. Thus, the current standard of care should restrict surgery to refractory cases that have failed non-invasive treatment and the principles outlined under the concept of "shared decision making" should be carefully applied [101, 102].

Recommendations for future research

Our comprehensive review of the literature addressing ILO has highlighted a paucity of reliable data in this important field of respiratory medicine. This limits our ability to provide robust clinical statements and/or recommendations and at the current time, this applies to all aspects of ILO, including understanding of the pathophysiology and aetiology, diagnostic approach and optimal treatment and surveillance practice. In addition, there is no clear-cut definition or reliable and reproducible diagnostic scoring or assessment system for this condition, opening a real risk of diagnostic imprecision. Our understanding of ILO thus remains at an early stage, which is concerning given its high prevalence, *i.e.* EILO reported in up to one in 10 young people. This task force has assessed and summarised the best available data to produce statements outlining current clinical practice, and to serve to identify key areas for future research.

It is highly unlikely that ILO is a single disease entity. Our current understanding of ILO rests on typical images of a decreasing size of the laryngeal inlet obtained during typical symptoms. These images can tell us the extent of laryngeal narrowing relative to some baseline measurement obtained in patients. The images do not enable measurement of the absolute laryngeal size, information that is needed to clarify what is an abnormal *versus* a normal or even an optimal laryngeal size for any given body habitus, functional level or sex. The images also do not tell us what should be considered a pathological narrowing when symptoms do occur, either at rest as in irritant ILO, or with increasing minute ventilation as in exercise ILO. Thus, techniques that enable objective assessment of the size of the laryngeal lumen with simultaneous full visual representation would be highly valuable, and appear to be an important first priority to move the field forward. Such techniques should be accurate and reproducible, applicable in any provocation setting, including exercise, and should not alter laryngeal dynamics, the very object of the assessment. Knowledge of the pressure drops and gradients over the laryngeal entrance area, *i.e.* from the epipharyngeal *via* the supraglottic, midglottic, glottic and subglottic spaces would contribute to the understanding of what structures are causally involved in eliciting and perpetuating symptoms, particularly in exercise ILO. Given the discomfort of laryngoscopy, most studies of laryngeal function have been performed in patients reporting symptoms, often with an insufficient number of healthy controls. Thus, we need more information on the range of normality, applying accurate and reproducible tests in heterogeneous groups that are large enough to serve as normative populations. Such datasets can aid the development of computer-based simulation programmes that will increase our level of understanding and

enable better predictions of effects from treatments. Given the discomfort and the resource-intensive nature of laryngoscopy, the development of less invasive or surrogate diagnostic methods is an obvious goal. However, at present, techniques that omit laryngoscopy seem unlikely to enable a distinction between glottic and supraglottic ILO, which is essential for further treatment and handling, particularly if laser supraglottoplasty is considered. The heterogeneity of findings reported from recent studies indicate that better phenotypic classification can facilitate individually tailored treatment, and indeed increase the success rates for treatment modalities other than surgery. These are all obvious issues to target in future research.

The role of psychological factors is controversial, probably reflecting the lack of an evidence base, including truly objective diagnostic tests. Thus, the role played by factors such as past and present stress, psychological factors, personality traits and even mental disorders need to be addressed in future carefully designed studies.

Future treatment studies must acknowledge the complex nature of laryngeal form and function in health and disease, and must categorise the patients carefully. Studies should at least discriminate between ILO occurring at rest and during exercise, and whether glottic or supraglottic structures are primarily involved. In particular, the place of surgery in these patients needs to be addressed in randomised controlled trials.

Concluding remarks

The aim of this task force document was to provide a concise state-of-the-art overview of the current research evidence evaluating ILO. This appraisal process and summary document has highlighted the fact that ILO is an important and prevalent entity and has considerable clinical impact for those affected with the condition. However, it is clear from our review that despite considerable progress and an evolving and strengthening evidence base within this field, our understanding of many aspects of ILO remains at a relatively embryonic stage. Specifically, our understanding of the aetiology and pathophysiology remain

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BOX 1 Summary of recommendations for future research

Develop a valid, reproducible and accurate diagnostic test for ILO that does not alter laryngeal dynamics and is widely applicable as a gold standard
Uncover aetiology and pathophysiological mechanisms
Determine the range of normal variation
Examine heredity and genetic factors and predispositions
Develop validated screening tools and more easily available diagnostic surrogate tests
Develop standardised speech and language therapy and respiratory physiotherapy interventions
Develop targeted pharmaceutical and surgical interventions based on pathophysiological components
Test interventions in adequately powered randomised controlled trials
Establish prevalence in unselected populations outside of Scandinavia
Update nomenclature as the field progresses
Form guidelines for diagnosis and treatment

BOX 2 Key facts

ILO most commonly presents as exertional dyspnoea, but can present with ambiguous symptoms and signs, particularly when coexisting with other conditions
Symptoms are most often limited to the inspiratory phase; rarely to the expiratory phase
At present, visualisation of the larynx during ongoing symptoms is the only objective way of making a complete anatomical diagnosis
Spirometry and other surrogate tests have poor sensitivity and specificity, but might provide useful clinical clues
Clinical signs of ILO include:
  Self-limiting intermittent dyspnoea triggered by specific exposures or (more rarely) occurring at random
  Wheezing or stridor (can be absent or difficult to distinguish from normal heavy breathing during intense exercise)
Likely triggers include (but are not limited to):
  Exercise
  Chemicals and odours
  Anxiety and psychological stress
Management options include speech and language therapy, respiratory physiotherapy, inspiratory muscle training, various medicinal remedies and supraglottoplasty, and additionally, the optimisation of treatment of any relevant comorbidity

poor and despite considerable technological advances, robust, validated, diagnostic and treatment algorithms are yet to be established. Remarkably, there are currently no randomised controlled studies evaluating therapeutic interventions in ILO. Overall, our appraisal process has acted to highlight a number of important deficiencies in current knowledge in the field, and to present a number of key research priorities with the main aim of helping to improve our understanding to afford improved care to individuals suffering with ILO.

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