Exercise-induced laryngeal obstruction

Prevalence, laryngeal findings and evaluation of treatment

KATARINA NORLANDER
Exercise-induced laryngeal obstruction (EILO) is one of many different causes for adolescents to experience dyspnoea during exercise. Objective exercise-testing with continuous video laryngoscopy is crucial for a correct diagnosis since it is difficult to differentiate EILO from other exercise related conditions in the airways only on the symptomatology. The main symptom in EILO is inspiratory stridor arising from an obstruction at the laryngeal level during ongoing exercise which quickly resolves after the exercise has stopped. EILO is often misdiagnosed as exercise-induced bronchoconstriction (EIB), which is obstruction in the peripheral airways that typically arises after cessation of exercise.

From a previous survey investigating self-reported exercise-induced dyspnoea in all 12-13-year-old adolescents in Uppsala (n=3,838, response rate 60.2%) a subset of 150 randomly selected adolescents (103 with dyspnoea and 47 controls) performed standardized treadmill exercise-tests for EIB and EILO.

During the exercise-test for EIB the subjects breathed dry air according to the current recommended guidelines. EIB was defined as a decrease in FEV1 ≥10% from baseline. EILO was diagnosed during a continuous laryngoscopy exercise (CLE) test by use of the CLE-score method and was defined as an obstruction of grade 2 at either glottic or and supraglottic laryngeal level. The estimated prevalence of EIB in the general population was 19.2% and the estimated prevalence of EILO was 5.7%. No gender differences were detected.

A diagnostic software program for EILO, EILOMEA, was compared with the CLE-score and the methods were found to be compatible. EILOMEA was used to map and compare laryngeal response patterns in adolescents with exercise-induced dyspnoea (EIB and/or EILO), in adolescents with dyspnoea but without a diagnosis of EIB or EILO, and in healthy controls, all of whom had performed the CLE-test. No differences were seen between the healthy controls and the adolescents with dyspnoea without a diagnosis. Only adolescents diagnosed with EILO showed a significant different laryngeal response pattern which strongly suggests that the diagnostic procedure is reliable.

In a follow-up study of patients referred for investigation of exercise-induced dyspnoea, we investigated the outcome of surgical vs. conservative treatment of EILO-positive subjects and subjects tested negative for the diagnosis, regarding the level of exercise-induced dyspnoea and physical activity. Surgically treated patients had less breathing problems and were more physically active than both conservatively treated patients and patients who were tested negative.

Keywords: Exercise, laryngeal obstruction, bronchoconstriction, CLE-score, EILOMEA

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To my family

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


* Shared first authorship


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Additional publications during my PhD studies which are not included in this thesis


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## Abbreviations

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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CLE-test</td>
<td>Continuous laryngoscopy exercise test</td>
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<td>CT</td>
<td>Conservatively treated</td>
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<td>EIA</td>
<td>Exercise-induced asthma</td>
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<td>EIB</td>
<td>Exercise-induced bronchoconstriction</td>
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<td>EILO</td>
<td>Exercise-induced laryngeal obstruction</td>
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<tr>
<td>EVH</td>
<td>Eucapnic voluntary hyperventilation</td>
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<tr>
<td>FEV$_1$</td>
<td>Forced expiratory volume in one second</td>
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<tr>
<td>PCA</td>
<td>Posterior cricoarytenoid muscles</td>
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<tr>
<td>ST</td>
<td>Surgically treated</td>
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<td>VCD</td>
<td>Vocal cord dysfunction</td>
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Introduction

When I started to work in the Ear-, Nose and Throat department in Uppsala in 2006 the first investigations of a new, somewhat mysterious group of patients, often young women, had just begun. These patients had been referred to our clinic for breathing difficulties during exercise when previous investigations had not led to any diagnosis, or prescribed asthma medication therapy had not resulted in expected symptom relief. That same year, 2006, Heimdal et al. published a paper describing the continuous laryngoscopy exercise test. It enables visualization of the larynx through flexible transnasal fibre-optic laryngoscopy so that we can actually see what happens in the larynx during ongoing exercise (1). Often observed in the patients was an obstruction of the laryngeal inlet during exercise that disappeared shortly after cessation, a condition now known as exercise-induced laryngeal obstruction, EILO.

During the last decade, the recognition and knowledge about EILO has increased but there is still very much we don’t know. As an extension of a previous study on the prevalence of exercise-induced dyspnoea in a general adolescent population, we investigated the prevalence of EILO as well as the prevalence of exercise-induced bronchoconstriction (EIB), by letting adolescents perform standardized exercise tests. Further, two different methods to diagnose EILO were compared and subsequently used to assess laryngeal response patterns during exercise in adolescents with and without dyspnoea. Finally, the outcome of surgical treatment of patients referred to our clinic has been analysed.

The studies in this thesis is an effort to add further scientific knowledge about EILO. I hope that it will inspire to further exploring of this, in many ways, young research field.
Background

Inducible laryngeal obstruction is a new consensus term which includes disorders known in the literature as vocal cord dysfunction, paradoxical vocal fold movement, induced laryngomalacia and many others. The consensus term underlines that an external stimulus is involved (2) and with the use of a prefix, a specific inducer to the laryngeal obstruction is pointed out. Hence, when exercise is the inducer the condition is called exercise-induced laryngeal obstruction.

Exercise-induced laryngeal obstruction, EILO

Laryngeal obstruction during exercise is not one, single diagnosis. Instead, EILO consist of a group of conditions in which airflow is hampered at the laryngeal level only during exercise, never at rest. The obstruction can be observed by performing continuous laryngoscopy during exercise (1). There are two main subtypes of EILO. The glottic type involves abnormal adduction or paradoxical movements of the vocal cords. The supraglottic type comprises an inward collapse of anatomical structures above the vocal cords; aryepiglottic folds, cuneiform tubercles and sometimes the epiglottis (3). The supraglottic type, often combined with a secondary glottic obstruction, is the most common type (4) (figure 1). This is in contrary to what has long been expressed in the literature, where the glottic type has been considered more prevalent and often been referred to as vocal cord dysfunction (VCD) (5, 6).

Exercise-induced bronchoconstriction, EIB

In the literature, dyspnoea during exercise is often referred to as exercise-induced asthma (EIA). In this thesis, we have investigated exercise-induced bronchoconstriction (EIB). Distinguishing between EIA and EIB is a complex task. When exercise triggers bronchoconstriction and exacerbation of asthma symptoms in a patient with asthma, it is called EIA. EIB on the other hand, can be diagnosed if the patient has no evidence of asthma except during or after exercise (7). This thesis will focus on EIB in the context used by Weiler et al. as a transient narrowing of the lower airways following exercise in the presence or absence of clinically recognized asthma (8).
Brief historical summary of the diagnosis of laryngeal obstruction

The term “inducible laryngeal obstruction” was formally accepted only a few years ago (1), but inspiratory wheeze as a possible symptom of obstruction has been described and discussed for more than a century. Many different terms have been presented trying to explain the trigger or the mechanism behind the obstruction, but for a long time it was considered to be of psychological origin only. Dunglison reported hysterical croup in women 1842 (9), MacKenzie described paradoxical vocal cord movements in hysterical adults 1869 (10), and in the beginning of the twentieth century, William Osler wrote about spasm of the laryngeal muscles due to hysteria (11). MacKenzie was first to describe direct laryngoscopy as an examination method (10). With the development of the fibre endoscopic technique, starting with Shigeto Ikeda in 1966, the larynx could easily be studied during symptoms. However, the main theory during the 1970s and 1980s was still that the trigger was psychological (12, 13). In 1983 Christopher et al wrote about vocal cord dysfunction presenting as asthma (5). A supraglottic obstruction instead of a glottic obstruction was first described by Lakin et al in 1984. By letting the subject run on a treadmill before laryngoscopy they identified exercise as a trigger (14). Laryngoscopy during exercise was performed on a stationary bicycle in 1996 (15) and four years later Naito let twelve persons perform various exercises, like playing tennis against a wall, with a fibre-optic laryngoscope inserted in the nose and fixated to an ordinary motorcycle helmet (16). Today we investigate EILO with the continuous laryngoscopy exercise test developed by Heimdal et al (1). The test is described in detail later in this thesis.
The complexity of the dyspnoea-problem

Prevalence of exercise-induced dyspnoea

Exercise-induced dyspnoea is common among children and adolescents (17-19) and a correct diagnosis is a challenge for the clinician (14, 20). EIB and EIA are common causes of exercise-induced dyspnoea and these diagnoses should be investigated (8). EILO must also be considered early in the diagnostic process since symptoms of EIB/EIA and EILO can be very similar.

Sometimes respiratory symptoms are due to poor physical fitness. In a prospective survey Seear et al found poor physical condition among 12 out of 52 children (23%) referred for poorly controlled asthma (21). In a retrospective study, Abu-Hasan et al found about the same percentage (22).

Prevalence of EIB

The American Academy of Allergy, Asthma & Immunology Work Group report from 2007 states that up to 90% of patients with asthma (varying ages) have EIB (23). The prevalence of asthma also tends to increase globally (18). The prevalence of EIB has been investigated in several studies and ranges between 7-16% depending on examination method and study population (24-28). The diagnosis is however too often based solely on observed symptoms (29) a strategy which has been shown to have poor sensitivity and specificity (27). Perceived dyspnoea symptoms do not correlate well with objective measures (30). Among athletes, the prevalence of EIB has been found to vary a lot in different studies. When eucapnic voluntary hyperventilation (EVH) has been the diagnostic method, numbers between 3-25% have been reported (31, 32). Gender differences towards a predominance of females have been reported in some studies (24, 27).

Prevalence of EILO

The prevalence of EILO is not well known. In an unselected cohort of 556 persons in Copenhagen aged 14-24 years, whereof 97 performed an exercise test with simultaneous laryngoscopy, the estimated prevalence in the general population was 7.5% (33). Morris et al. did a study including 40 militaries with exertional dyspnoea and twelve healthy controls. Fifteen percent of the patients had laryngeal findings consistent with vocal cord dysfunction. The assessment, however, was made with laryngoscopy before and after exercise but not during the actual effort (34). EILO prevalence has been found to be as high as 35% among athletes but the study population was highly selected (35).

Most patients referred to our clinic for investigation are young females, median age 16.5 years. Many studies report that EILO is more common in young females than males (4, 33, 36-38).
Complicating factors

There are several factors that complicate the interpretation of previous studies regarding the prevalence of EILO, in analogy with what was previously described for EIB. The heterogeneity regarding inclusion criteria, diagnostic methods, diagnostic criteria and terminology used to describe laryngeal findings makes it almost impossible to get an overview. Referral bias is a problem since most studies take place in tertiary settings.

It is important to remember that stridor, high-pitched noisy breathing, is a symptom, not a diagnosis. Røksund et al examined 166 patients with continuous laryngoscopy during exercise and were not able to link inspiratory stridor to a single causal factor, or to a specific structure in the larynx (4). More than 80 different terms can be found in the literature that describe respiratory problems at the laryngeal level (39). In many studies where the term vocal cord dysfunction has been used, we know today that what is described in many of the cases probably is what we now call EILO.

The importance of correctly diagnosing exercise-induced dyspnoea and its different causes

EIB is common among asthmatics, and EIB can coexist with EILO (40). Also, asthma and EILO can coexist (37, 41). In line with earlier described problems dealing with terminology and diagnostic methods, it is difficult to know how common coexistence between asthma or EIB and EILO is. Many studies describe inspiratory stridor and label it as VCD. Sometimes laryngoscopy has been performed during symptoms that have not been triggered by exercise (42), sometimes after exercise has stopped (6) and sometimes laryngoscopy has not been done at all (43). To investigate coexistence, strict and accurate diagnostic procedures must be used since the symptoms, at least for the observer, are very similar (5). From the patient’s history alone it is very difficult to tell if it is EILO or EIB since patients seldom can pinpoint if their respiratory distress originates in the central or the peripheral airways. Most of them just describe “dyspnoea”. Unfortunately, the recommended diagnostic requirements are often not met (32).

EIB appears to be over-diagnosed frequently which is very unfortunate (44). A correct diagnosis of asthma, EIB or EILO provides the possibility to offer targeted treatment, but equally important is to cease unnecessary medical treatment for asthma if the person has EILO (45). The symptom similarity of EIB and EILO often leads to the misunderstanding that the patient suffers from “refractory asthma” and the EILO-diagnosis is delayed (46, 47).

Children and adolescents with exercise-induced dyspnoea are reported to have reduced health related quality of life, lower physical activity level, poor sleep and higher school absenteeism (17, 48). Furthermore, participating in sport activities can be important from a social point of view (49).
The airways

The airways are anatomically divided into the upper, extrathoracic airways and the lower, intrathoracic airways. The larynx forms the boundary between the upper and lower airways and the narrowest part of the upper airways is at the level of the vocal cords.

Anatomy of the larynx

The larynx is built up by several cartilages, joints, small muscles and ligaments. It extends from the tip of the epiglottis to the inferior border of the cricoid cartilage, which is a circular cartilage anchored to the trachea. The larynx can be described as a narrow funnel. The anterior border consists of the thyroid cartilage and the epiglottis. Epiglottis is, as is the whole interior of the larynx, covered by mucosa. From the lateral borders of the epiglottis, the mucosa extends posteriorly forming the aryepiglottic folds. The posterior border is in the intraarytenoid notch. The small triangular arytenoid cartilages are placed upon the cricoid plate and regulated by the arytenoid muscles, enabling abduction (via posterior cricoarytenoid muscles) and adduction (via lateral cricoarytenoid muscles) of the vocal cords. Other cartilages in the larynx are the cuneiform and the corniculate cartilages (50) (figure 2).

The laryngeal interior is divided into three levels: the supraglottic, the glottic and the subglottic level. This is important to keep in mind for the understanding of EILO.

Figure 2. Larynx from above.
Airway physiology at rest

Inside the chest there is normally a negative pressure at rest, i.e. negative intrathoracic pressure. Inhalation, which is an active process, is initiated by the diaphragm and the external intercostal muscles. When the diaphragm contracts it is pulled downwards. Simultaneous contraction of outer intercostal muscles pull the sternum and ribs upward and out. This combined actions cause the thorax to widen and, due to the negative intrathoracic pressure, air will flow in through the nose, and mouth, if it is open. The air is conducted through the pharynx, larynx, trachea and bronchi to the alveoli where gas exchange occurs. At the end of inhalation, the lungs are filled with air and expanded. The elasticity of the lung tissue then causes the air to flow out passively during expiration when the diaphragm and outer intercostal muscles return to their resting position. If there is an obstruction in the lower airways, the passive airflow on expiration will be hampered consequently expiratory symptoms will occur (51, 52).

Normal laryngeal function at rest

The larynx is a complex organ with vitally important and highly evolved biological functions. It must serve as an open valve during respiration, as a partially closed valve during phonation and as a completely closed valve when it protects the lower respiratory tract against aspiration during swallowing. The vocal cords are controlled both voluntarily and by the autonomic nervous system, and therefore breathing can be affected through several different mechanisms: physiological, neurological and psychological.

During normal quiet breathing the glottis opens more during inhalation than exhalation (53). This movement of the vocal cords is due to a coordinated reflex between the posterior cricoarytenoid muscles (PCA) with other respiratory muscles, foremost the diaphragm. During inhalation, the PCA muscles are activated and the vocal cords are abducted shortly before the diaphragm starts to contract (53, 54). Due to this mechanism, but also because the vocal cords can be controlled voluntarily, the larynx functions as a valve regulating both pressure and airflow through the glottis. Since the PCA and vocal cords are ahead of other actions, and the glottis usually is narrower during expiration, a positive pressure will be maintained in the airways for a longer time during expiration which optimizes gas exchange (53). This neuronal reflex to narrow the glottic opening is augmented during bronchoconstriction (55).
Changes in lower airway physiology during increasing exercise

Exercise increases the body’s metabolic demands which will require a greater amount of oxygen. This requirement is met by several adaptations that increase the minute ventilation. Normal minute ventilation is 6-8 litres per minute at rest. The minute ventilation can increase by taking deeper breaths and/or increase the respiratory rate (56). Normal breathing rate at rest is 12-16 breaths per minute. During exercise, it can be as high as 30-40 breaths per minute and the minute ventilation subsequently increases 20 to 30 times (57). In elite athletes, minute ventilation can be over 200 litres per minute (57). To be able to breathe in more oxygen we change from nasal breathing to mouth breathing when minute ventilation reaches 25-30 litres per minute (58). Inhalation is also facilitated by activation of accessory respiratory muscles such as the sternomastoid and scalene muscles. Exhalation changes from a passive to an active process by activation of intercostal and abdominal muscles (59).

Changes in the larynx during exercise

When the respiratory rate increases, air passes through the larynx with a higher flow rate than at rest. At inhalation during hyperventilation the vocal cords are more abducted than during quiet breathing. During heavy hyperventilation, they are also abducted during exhalation which is beneficial as it reduces the flow resistance (60, 61).

The airflow exerts forces on the laryngeal tissues resulting mainly in a negative transmural pressure gradient which will cause the aryepiglottic folds to move medially during inhalation. These forces will be greater the more the airflow is increased (62). The larynx can be kept open because of its construction of rigid cartilages, strong ligaments and many small intrinsic and extrinsic muscles. At the supraglottic level, the epiglottis tilts anteriorly when these muscles are activated, and this tightens the aryepiglottic folds (15). At the glottic level, the vocal cords will lengthen and abduct due to increased activity in PCA (58, 59). While exercising, the glottic opening is increased mainly posteriorly during exhalation, leading to a reduction in airflow resistance (54).

When the airflow is increased, the relative contribution of upper airway resistance to the total airway resistance is increased (58). Gradually stronger forces acting on the laryngeal tissues result in correspondingly increased movements of the aryepiglottic folds. A mild adduction of the aryepiglottic folds is considered a normal response since it has been observed in healthy subjects (3, 15). At the glottic level, it has been suggested that a 50% narrowing of the glottis is needed for it to be pathological (42) but it is not yet thoroughly investigated. When extrathoracic airflow is hampered, as in laryngeal obstruction, inspiratory symptoms will occur (63).
Clinical features of EIB and EILO

EIB
Symptoms of bronchoconstriction include cough, expiratory wheeze, dyspnoea, chest tightness and increased mucus production. Severity of symptoms depends on intensity and effort and is modified by temperature and humidity in the inhaled air (8, 42, 64). Symptoms evolve shortly after the exercise session and reach maximum within 3-15 minutes (65). Symptoms generally last for 30-90 minutes in the absence of treatment (32). At physical examination, expiratory wheeze and a prolonged expirium is noted. Laryngoscopy during ongoing symptoms shows normal findings or a mild glottic adduction (55, 66).

EILO
Clinical examination of the larynx at rest is normal. Symptom onset is typically triggered by exercise requiring high ventilation (1). Respiratory distress can be observed.

In glottic EILO a very sudden onset is typical, due to an abrupt adduction of the vocal cords. Symptoms occur during the exercise. A prolonged inspirium is noted, often accompanied by inspiratory stridor of high frequency. Laryngoscopy during symptoms shows adducted vocal cords or paradoxical vocal cord motion (3).

In supraglottic EILO symptoms arise quickly, yet to some extent gradually. Symptoms increase with the workload and reach peak level at the end of the exercise session or during the first 2-3 minutes after stopping. It is the symptoms that forces the person to cease exercising and then symptoms disappear in a few minutes. At examination, a prolonged inspirium is noted, sometimes accompanied by an inspiratory wheeze of low frequency (4, 67). Laryngoscopy in a symptomatic person reveals collapse of supraglottic structures.

Diagnostic methods for EIB and EILO

EIB
Direct or indirect methods can be used to diagnose EIB. A direct provocation by inhalation of a provoking agent such as methacholine is used for detecting or ruling out bronchial hyperreactivity. A positive test strengthens the suspicion of underlying asthma. The recommended indirect method is an exercise test on treadmill or bicycle while the person is breathing dry air (32). The EIB-diagnosis is suggested if a decrease in $\text{FEV}_1 \geq 10\%$ on spirometry is noted after the test (32, 68). Another indirect method is EVH. It causes the airway mucosa
to dry out and creates a hypertonic environment, which is thought to be the aetiology behind EIB (69).

**EILO**

**Patients history**

Patients with EILO describe symptoms like shortness of breath, tightness in the throat and sometimes a sensation of suffocation and panic. Exercise must be recognized as the inducer to the breathing problems. The clinician should focus on distinguishing EILO from EIB and ask key questions about symptom onset, duration and how quickly the breathing problems subside after cessation of exercise. A sudden onset of respiratory distress during exercise in combination with a relatively short duration and absence of symptoms at rest points toward an obstruction at the laryngeal level. Whether symptoms occur during inhalation or exhalation is important information but often difficult for the patient to answer. During recent years, several questionnaires have been developed with the aim to facilitate clinical evaluation of dyspnoea and to differentiate VCD from asthma (70-72).

**Exercise test**

Treadmill is most commonly used for the exercise test but other modalities are possible (73, 74) on condition that the test subject can reach maximum exhaustion (75). The larynx is filmed continuously and the dynamic development of obstruction is observed. If breathing is hampered during inhalation and/or exhalation and how long it takes before the larynx normalizes after exercise has stopped is also noted (figure 3). Filming with sound enables a later, thorough analysis. Laryngeal findings at glottic and supraglottic level are assessed and scored according to the criteria by Maat et al (3). Since it is the effort that triggers the symptoms and the symptoms subside very quickly after the effort has ceased, it is not meaningful to perform a laryngoscopy either before or after exertion. Laryngoscopy during ongoing exercise is considered gold standard for diagnosing EILO (2, 4, 15, 61, 67, 73).

The scoring method by Maat et al is a validated method and the most widely used. This scoring method is described in detail later in this thesis. However, neither this method, nor any other proposed method for quantification of the laryngeal findings (76-78) are considered gold standard for setting the diagnosis.
Figure 3. Continuous laryngoscopy exercise test on treadmill. A fibre-optic laryngoscope is inserted through the nose, fixated in a specially designed helmet and connected to a camera. The tip of the laryngoscope is placed just above the epiglottis to provide a detailed view of the larynx.

**Lung function test**

Spirometry is described as a diagnostic method of investigation. A truncated inspiratory flow-volume curve has been observed in studies on patients with stridor (14, 42) but since stridor can have other causes this information is of little value. The method is also highly dependent on the patient’s cooperation (37). Another study evaluated flow-volume loops before and after exercise and it showed that spirometry cannot be used as a diagnostic tool for EILO (79). However, lung function tests are valuable in the investigation for comorbidities like asthma.

**Other provocation tests**

EVH has been shown to induce both glottic and supraglottic obstruction (80). Methacholine and mannitol (81, 82) as well as histamine (76, 83) have been tested in the same way as for bronchoconstriction with no significant results. On the contrary, it is not possible to draw any conclusions of a positive methacholine challenge test since it is also used to investigate asthma.

A great disadvantage with all methods except direct visualization of the larynx is that no information is obtained about the location of the obstruction, i.e. if it is a glottic or a supraglottic obstruction.
Aetiological aspects of EILO

The aetiology for EILO has not been established. Since laryngeal obstruction can occur at different levels, several theories have been suggested. A review of the literature reveals a complexity that is more complicated than that there is just one, single trigger (exercise), that would cause the typical breathing problems and laryngeal findings in EILO. The presence of a co-morbidity could lead to a laryngeal hypersensitivity, leading to that a lower amount of stimulus, which in the normal case would not trigger breathing problems, will do so in that context (84). Breathing problems can be further aggravated if the response to the stimulus is disproportionately large (85). Asthma and gastro-oesophageal reflux are the most studied conditions that have been associated with EILO. It is therefore possible that EILO in some cases are caused by one mechanism alone, and in other cases by a combination of aerodynamic mechanisms, laryngeal pathophysiology and co-morbidity.

Aerodynamic forces

The larynx is, as earlier described, the narrowest part in the upper airways. When airflow increases, so does the forces acting on the laryngeal tissues. A possible explanation for supraglottic EILO could be that the supporting structures no longer manage to keep the arytenoid cartilages and the plicae aryepiglottica in an upright position, which results in a supraglottic collapse. When the opening for the airflow gets smaller the velocity of the airflow increases according to Poiseuille’s law. This leads to an even greater negative pressure that may affect the vocal cords and give rise to a secondary glottic obstruction (4, 38).

Impaired neurological function

The glottic closure reflex protects the lower airways against aspiration and can be triggered by chemical stimuli or air puff stimuli (81, 86). Hyperventilation during exercise could theoretically elicit the reflex. Gastro-oesophageal reflux could possibly act as a chemical trigger but studies are inconclusive whether reflux leads to a more easy-triggered reflex or in fact desensitizes the laryngeal receptors (87).

Psychological factors

There are different views on whether psychological factors, for instance a panic attack, causes breathing problems in EILO, or if the panic attack is a response to severe breathing problems during exercise. Since EILO for a long time was considered to be only a vocal cord dysfunction problem, and because diagnosis in most cases was made without proper endoscopic examination during exercise, the predominant view has been that psychological problems are either the main cause or a strong contributor (42, 46, 88-92). When endoscopic examination of the larynx during exercise has been performed, panic
attacks or stress reactions has been noted after the obstruction occurs, which strengthens the reverse opinion (4, 38). However, stress as a trigger cannot be completely ignored, as psychological factors always can play a role in all situations.

**Treatment for EILO**

The starting point for treatment is a correct diagnosis where untreated co-morbidities have been excluded. For both glottic and supraglottic EILO it has been reported to be of great value to the patient to receive thorough information about the origin of symptoms and to have an opportunity to see the recording of the laryngeal findings obtained during the CLE-test (38, 75).

**Glottic EILO**

The psychological view has greatly influenced treatment. The pressure “to perform” has been stressed as a contributing factor among athletes. Individual support and counselling have dominated (93). Psychotherapy (5, 94) and hypnosis (95) have been suggested. Speech therapy with the aim of learning to relax the laryngeal muscles (96, 97) and to master different breathing techniques (5, 98-100) have been reported to be effective but no controlled studies have been done. Neither the placebo effect nor how different breathing techniques should be performed during exercise have been taken into proper consideration.

Doshi reported that Atrovent (Ipratropium) oral inhaler before exercise could prevent exercise-triggered VCD in six patients (101). Inspiratory muscle training (IMT) is believed to strengthen PCA (102, 103) in subjects with laryngeal obstruction but it remains to be proven. In healthy subjects, IMT has been shown to have effect on abduction of the vocal cords (104). Anti-reflux therapy has been tried, however not specifically for glottic obstruction occurring during exercise (105).

**Supraglottic EILO**

Both speech therapy and breathing techniques are tried at some centres (108) but no long-time follow-up results exists. Surgery (laryngoplasty) involves reduction of the aryepiglottic folds to prevent them from covering the laryngeal inlet (38, 106, 107) (figure 1 and 2). The supraglottic subtype must be verified endoscopically during an exercise-test before surgery.
Aims of present studies

To analyse the consistency between CLE-score and EILOMEA, two diagnostic methods for laryngeal obstructions (I)

To investigate the prevalence of EIB and EILO in adolescents with and without self-reported exercise-induced dyspnoea (II)

To map and compare movements of glottic and supraglottic anatomical structures in healthy adolescents and adolescents experiencing dyspnoea during strenuous exercise (III)

To investigate the robustness of diagnostic methods for EILO (I-III)

To evaluate surgery as a treatment for severe cases of supraglottic EILO regarding self-reported exercise-induced breathing problems (IV)

To investigate how symptoms and physical activity change over time in patients with EILO who have undergone surgery, in patients with EILO treated conservatively and in patients tested negative for EILO at CLE-test (IV)
Methods

Ethics

All studies were approved by the Regional Ethics Board at the Medical Faculty at Uppsala University, Uppsala Sweden (Dnr 2010/107 (I), Dnr 2011/413 (II-III), Dnr 2011/208 (IV)). Informed written consent was obtained from all participants and their guardians in study II-IV. According to the Ethics Review Board, no written consent was needed for study I since it was a methodological study of unidentifiable endoscopic laryngeal recordings where no personal data was exposed.

Table 1. Overview of studies included in this thesis.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Objective</th>
<th>Design</th>
<th>Data used for analyses</th>
<th>Dropouts or excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>60</td>
<td>Comparison of CLE-score and EILOMEA methods</td>
<td>Method comparison</td>
<td>CLE-scores and measurements from laryngeal recordings</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td>150</td>
<td>Prevalence of EIB and EILO</td>
<td>Observational Descriptive Cross sectional</td>
<td>Outcome of EIB- and CLE-tests</td>
<td>25</td>
</tr>
<tr>
<td>III</td>
<td>125</td>
<td>Laryngeal movements during exercise in controls and dyspneic subjects</td>
<td>Observational Descriptive Case-control</td>
<td>CLE-scores and measurements from laryngeal recordings</td>
<td>46</td>
</tr>
<tr>
<td>IV</td>
<td>84</td>
<td>Impact of ST, CT and a negative diagnosis on exercise-induced dyspnoea and physical activity</td>
<td>Observational Follow-up</td>
<td>Self-reported exercise-induced dyspnoea and physical activity</td>
<td>25</td>
</tr>
</tbody>
</table>

Dropouts or excluded: 7 25 46 25
Total analysed: 53 Anonymous 125 Controls n=42 Dyspnoea n=83 79 Controls n=28 Dyspnoea, no diagnosis n=31 EIB n=10 EILO n=10 59 ST n=14 CT n=17 Tested negative n=28

ST = surgically treated, CT = conservatively treated
Diagnostic procedures
EILOMEA (paper I and III)
EILOMEA is a validated, diagnostic, software measuring tool developed to calculate the severity of an obstruction at the glottic or the supraglottic level (78). The rater chooses a still frame obtained from a laryngeal recording at a CLE-test which shows the maximum obstruction during inhalation. A set of points are plotted on the image which mark anatomical landmarks. A baseline is chosen where the plicae aryepiglottica turns into the epiglottis and hereafter both tuberculum cuneiforme, the anterior commissure, the vocal cords and the posterior wall between the arytenoid cartilages are marked (figure 4). The software calculates three parameters: the glottic angle at the anterior commissure between the true vocal cords, the glottic obstruction (obtained by dividing the area between the vocal cords by the anterior-posterior laryngeal distance) and the supraglottic obstruction (ratio between the actual lumen and the lumen at the level of the arytenoid region). Glottic obstruction is referred to as P-factor and supraglottic obstruction as C-factor.

Figure 4. Anatomical structures marked according to guidelines for EILOMEA
EIB-test (paper II)

The test for exercise-induced bronchoconstriction was performed according to current guidelines presented by the American Thoracic Society (32). All participants were instructed to cease short-acting β2-agonists 8 h before the test, long-acting β2-agonists 24 h before the test and leukotriene receptor antagonists 72 h before the test. On the day of the test no inhaled corticosteroids should be used. Within four hours before the test they should not perform vigorous exercise, eat heavy meals or use nicotine or caffeine containing food or beverages.

The test was performed by letting the adolescent run for 6 minutes on a treadmill while wearing a nose clip and breathing dry air through a tube. The treadmill speed and slope was adjusted individually so that all participants reached 90% of predicted maximum heart rate (109) within the first 1.5 minutes and maintained this exercise load throughout the test. Baseline spirometry was measured following recommended guidelines (110) both before running and repeatedly after the test. EIB was defined as a decrease of ≥10% in FEV₁ from baseline in at least one measurement during a 30-minutes time span after the test.

CLE-test (paper II)

Prior to the test all participants were informed that there were no restrictions regarding asthma medication, meaning that those who normally use asthma medication before physical exercise should do so also before the CLE-test. They were instructed to avoid vigorous exercise on the day of the test and heavy meals within four hours before the test.

The test was performed according to the procedure described by Heimdal et al (1). Before the test, naphazoline-lidocaine was sprayed twice into each nostril to achieve local anaesthesia and dilatation. After warming up for two minutes, the treadmill was stopped and a fibre-optic laryngoscope was inserted in one nostril so that the tip of the laryngoscope was placed just above the epiglottis, providing a detailed view of the larynx. The laryngoscope was fastened in a specially designed helmet so that it stayed in position, and then it was connected to a camera. The participant started to run at a speed of 9 km/h with no inclination and the speed was increased by 1 km/h every minute until 13 km/h. Hereafter the inclination was increased by 2% every minute. The participants were instructed to run until breathing problems forced them to stop, or if no breathing problems occurred, until exhaustion. For the test to be considered successful, the heart rate had to reach ≥90% of predicted maximum (110). The larynx was filmed continuously and laryngeal findings were graded at moderate and maximum effort according to the CLE-score method (3). The upper body was recorded using an external camera that also filmed the monitor showing the larynx (figure 3). An obstruction of grade 2 or more
at either the glottic or supraglottic level was considered a positive response and was defined as EILO.

CLE-score method (paper I-IV)

The CLE scoring method is an assessment tool developed for assessing the dynamic behavior of anatomical structures in the larynx during exercise, from moderate effort to exhaustion (3). When scoring is made during inhalation in a representative breathing cycle it allows evaluation of presence, type and severity of both glottic and supraglottic obstruction. The degree of glottic adduction and medial rotation of the aryepiglottic folds are assessed separately, each on a four-graded scale ranging from 0 to 3, where 0 represents no obstruction, 1 is mild, 2 is moderate and 3 is severe obstruction (figure 1). An obstruction score of 2 or more at either level is considered diagnostic for EILO. Assessments are made at two separate moments during the CLE-test; at moderate effort within 1 minute from start, and at maximum effort shortly before the test person stops due to exhaustion or respiratory distress.

In study I, II and IV, only the CLE-scores at maximum effort have been used. In study III, CLE scores from both time points have been used. Scoring has been made in real time during CLE-tests (study II and IV), and from video recordings obtained at earlier CLE-tests (study I and III).

Study populations/Material and Design

Paper I

Study material

Sixty anonymous laryngeal recordings obtained from previously performed CLE-tests in three Scandinavian centres were used. Each centre submitted 20 laryngoscopic recordings, purposely chosen to reflect cases with varying combinations and severity of glottic and/or supraglottic obstruction and varying quality of the recordings, including compressed file format (i.e. lower resolution of the picture).

Study design

Using their respective method, the developers of the CLE score method (3) and the EILOMEA method (79) evaluated the recordings. The developers assessed each recording once and were blinded both to the history of the patients and to each other’s assessments. Correlation between assessments made with the two methods were investigated.
Papers II-III

Background data
All 12-13-year-old adolescents (born 1997-1998) in the city of Uppsala (n=3,838) were invited to participate in a survey investigating exercise-induced dyspnoea (19). The response rate was 60.2% (n=2,309) whereof 1,136 were females. No differences were seen regarding age, gender, body mass index and postal area codes between the adolescents who responded and those who did not. An affirmative answer to the question “Have you had an attack of shortness of breath that came following strenuous activity at any time in the last 12 months?” (111) classified the adolescent as dyspneic (n=330), and a negative response as a healthy control (n=1,979).

Study population
In study II the study population consisted of 150 adolescents invited to perform exercise tests. A total of 146 adolescents completed an EIB-test and 125 completed both an EIB- and a CLE-test, 83 with dyspnoea and 42 controls.

In study III the study material consisted of laryngeal recordings from the 125 adolescents who had completed both tests.

Study design Paper II
Results from the survey regarding dyspnoea showed a female-male ratio of 3:2. A stratification for these gender differences was made and two randomly ordered lists were created, one with adolescents with dyspnoea and one with healthy controls. The exclusion criteria were pulmonary disease apart from asthma, cardiac co-morbidity or a functional disability that resulted in inability to perform exercise tests. By random selection, 199 adolescents with dyspnoea and 123 controls were invited to perform two separate exercise tests to diagnose or exclude EIB and/or EILO.

A total of 103 adolescents with dyspnoea and 47 controls accepted to participate. In both groups, there were more adolescents that had reported physician diagnosed asthma who chose to participate, compared to adolescents who declined participation. No other differences were detected between the groups. Group characteristics are presented in table 2.

At a first clinical visit, a research nurse informed all participants individually about forthcoming exercise-tests for EIB and EILO and how to prepare for them.

At a second visit the adolescents performed a standardized EIB-test on treadmill with inhalation of dry air (8). It was performed on average a median (IQR) of 12 (2-19) days after the pre-test visit and the investigator who collected the data was blinded to whether the participants belonged to the exercise-induced dyspnoea group or the control group. Four adolescents with dyspnoea declined participation in the EIB-test.
Table 2. Characteristics of participating adolescents and adolescents declining participation in study II. Results presented as mean ± SD and n (%).

<table>
<thead>
<tr>
<th></th>
<th>Exercise-induced dyspnoea</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participating adolescents</td>
<td>Declining participation</td>
</tr>
<tr>
<td>Age</td>
<td>13.7±0.66</td>
<td>13.7±0.66</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.4±2.6</td>
<td>19.4±2.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>49 (47.6)</td>
<td>31 (32.2)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>29 (28.3)</td>
<td>30 (31.3)</td>
</tr>
<tr>
<td>Current wheeze</td>
<td>57 (55.3)</td>
<td>47 (49)</td>
</tr>
<tr>
<td>Day time dyspnoea</td>
<td>17 (16.5)</td>
<td>9 (9.4)</td>
</tr>
<tr>
<td>Nocturnal dyspnoea</td>
<td>27 (26.2)</td>
<td>20 (20.8)</td>
</tr>
</tbody>
</table>

At a third visit the adolescent performed a CLE-test on treadmill (1). The test was performed on average a median (IQR) of 38 (22-66) days after the EIB-test. The investigator was not the same person who had conducted the EIB-test and was blinded to whether the participants belonged to the exercise-induced dyspnoea group or the control group, as well as to the EIB test result. Out of 146 adolescents who had performed the EIB-test, 19 (14 with dyspnoea) declined participation in the CLE-test. Another two adolescents from the dyspnoea group was excluded while doing the test, one due to equipment failure of the recording and one due to fainting shortly before the test when the laryngoscope was inserted. An overview of the design and participants in each step are presented in figure 5.
Figure 5. Participants inclusion and exclusion in study II.
Study design Paper III

Not all tested adolescents were found to have EIB or EILO. Scoring results from adolescents in the control group and the exercise-induced dyspnoea group without a diagnosis was examined further. The laryngeal films recorded during the CLE-tests were anonymized and coded so that the investigator was blinded to whether the adolescent had stated breathing problems or not. Films were excluded due to poor visualization of laryngeal structures or if there was no endoscopic recording at all, only an external film with the larynx visible on the monitor beside the test subject (figure 3).

A still frame was chosen from the film for each subject both at moderate effort and at maximum effort, i.e. at the same time points as when the CLE-scoring had been done. The still frames were assessed in random order and measurements were made three times on each still frame using the software measuring tool EILOMEA (78). Mean values for the glottic angle, glottic obstruction (P-factor), and supraglottic obstruction (C-factor) were calculated, as well as the difference between the mean values at moderate and maximum effort.

This procedure was repeated with films from adolescents who had been diagnosed with EIB and EILO. From the EIB group, only films from subjects that had not taken any asthma medication before the CLE-test were included. Study population and group characteristics are presented in table 3.

Table 3. Population and group characteristics of participants in study III. All data except for gender are presented as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Controls n=28</th>
<th>Exercise-induced dyspnoea n=31</th>
<th>EIB n=10</th>
<th>EILO n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>14.9±0.7</td>
<td>15.0±0.7</td>
<td>14.9±0.5</td>
<td>14.7±0.5</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>17 (61)</td>
<td>16 (52)</td>
<td>7 (70)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>20.3±2.4</td>
<td>20.9±3.4</td>
<td>20.5±2.5</td>
<td>21.5±3.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.4±8.8</td>
<td>169.1±7.5</td>
<td>166.8±10.4</td>
<td>169.3±9.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>59.3±10.9</td>
<td>60.0±11.4</td>
<td>59.9±5.8</td>
<td>61.9±13.3</td>
</tr>
</tbody>
</table>

Paper IV

Study population

The study population consisted of a cohort of 84 consecutive patients (69 females) referred for exercise-induced dyspnoea and CLE-tested during a four-year period. Forty-seven of the subjects were diagnosed with EILO and 37 had a negative test result. Out of the 47 EILO positive, 15 underwent surgical treatment during this period.
*Study design*

All patients answered a questionnaire at diagnostic CLE-test regarding exercise-induced breathing problems, current physical activity level and medical history of asthma and perennial allergy. To rate the symptom severity of the exercise-induced breathing problems, a visual analogue score (VAS) ranging from 0 (no breathing problems) to 10 (worst possible breathing problems) was used. Patients diagnosed with EILO received information about breathing exercises that might reduce symptoms and were invited to contact the investigating doctors by phone two months after the CLE-test and give a follow-up report on the effect. If breathing exercises were insufficient, the possibility of improvement by surgery were discussed with subjects having severe supraglottic EILO. Out of 27 subjects, 15 underwent laryngoplasty.

A follow-up questionnaire was sent to all subject 1-3 years after the diagnostic CLE-test (Appendix 1). The original questionnaire was supplemented with questions about whether the subject had changed physical activity level and/or type of sport. If that was the case, they were asked to specify if these changes were because of breathing problems or not. Patients were again asked to grade the severity of the breathing problems on a visual analogue scale. The responders were categorized as subjects with EILO who had undergone surgery, patients with EILO treated conservatively and patients who were tested negative for laryngeal obstruction (figure 6).

![Flowchart](image)

*Figure 6. Study IV. Participants and dropouts including EILO subtypes and number of patient who were offered and accepted or refrained surgery in each group.*
Statistical analyses

For all analyses, only two-sided tests were used and the selected critical statistical significance level was 95% (p<0.05).

Paper I
The EILOMEA method results were controlled for normal distribution and equal variances for each matching CLE-score. Differences in means of the EILOMEA measures were tested between each CLE-score grade using t-test. Analyses were performed using JMP statistical software version 11.1.1.

Paper II
Anthropometric data, lung function, asthma medication and exercise test results were summarized as means, standard deviations and minimum and maximum for continuous variables, and as numbers and percentages for categorical variables. Age, BMI and FEV₁ were compared between subjects using unpaired Student’s t-test. For all categorical variables, a cross tabulation vs subject groups were performed and subject groups were compared using Fisher’s exact test. The EIB and EILO prevalence estimates were based on the assumptions that the population strata with and without exercise-induced dyspnoea differed. Assuming that there was no selection bias, the dyspnoea stratum with exercise-induced dyspnoea was calculated from the rate of exercise-induced dyspnoea among responders multiplied by the population size, and the stratum without exercise-induced dyspnoea was assumed to represent the rest of the population. Tested adolescents were assumed to be random samples from the two strata. The prevalence estimate and 95% confidence interval were calculated according to the theory for stratified samples (112). Data were analyzed using Statistical Package for Social Science software v.21.

Paper III
All analyses were made at group level. Non-parametric Mann-Whitney U-tests were performed to compare groups two-by-two. Continuous variables were summarized as means and standard deviations. A regression analysis (95% confidence interval) was performed with change in percent from value at moderate effort to value at maximum effort as dependent variable and group, gender and value at moderate effort as independent variables.

Paper IV
Kruskal-Wallis test (non-parametrical ANOVA) was used to analyze if there was any difference between groups regarding symptom severity. If results were significant, Mann-Whitney U-tests were performed to compare groups two-by-two. Fisher’s exact test was used to compare adjusted physical activity level between surgically and conservatively treated EILO subjects. SAS software version 9.3 was used for the analyses.
Summary of results

Comparison of CLE-score and EILOMEA (paper I)
The CLE-score and EILOMEA method were compatible, showing significant
differences in the means for all EILOMEA measures corresponding to CLE-
score 1 vs 2 (mild vs moderate obstruction) and 2 vs 3 (moderate vs severe
obstruction). EILOMEA also distinguishes between CLE-score 0 and 1 (no
obstruction vs mild obstruction), regarding the glottis area (P-factor), but not
regarding supraglottic area (C-factor) or the glottic angle (table 4).

Table 4. Means, standard deviations and \(p\)-values for EILOMEA glottic angle and
glottic area for each glottic CLE-score, and for EILOMEA C-factor for each supra-
glottic CLE-score

<table>
<thead>
<tr>
<th>CLE-score</th>
<th>EILOMEA</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glottic obstruction</td>
<td>Glottic angle</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>48 (9)</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>45 (14)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>25* (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>13* (6)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Glottic obstruction</td>
<td>P-factor</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>64 (20)</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>48* (17)</td>
<td>0.0139</td>
</tr>
<tr>
<td>2</td>
<td>25* (8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>16* (8)</td>
<td>0.012</td>
</tr>
<tr>
<td>Supraglottic obstruction</td>
<td>C-factor</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.51</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>0.47 (0.09)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>0.34* (0.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>0.21* (0.12)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*Differed significantly from the mean of the CLE-score of the row above
Prevalence of EIB and EILO (paper II)

In the dyspnoea-group 42 adolescents (42.4%) were diagnosed with EIB and among the controls seven (14.9%) met the criteria for an EIB diagnosis. The estimated prevalence of EIB in the total population of 3,838 adolescents was 19.2% (95% CI 9.9;28.4), with no gender differences (18.6% in females and 19.7% in males).

EILO was diagnosed in nine (10.8%) adolescents in the dyspnoea group and two (4.8%) in the control group. The estimated prevalence of EILO in the population was 5.7% (95% CI 0.01;11.4) with no gender differences (5.7% in both females and males).

Among the dyspneic adolescents (n=83), EIB were found in 39.8%, and among the nine adolescents diagnosed with EILO, four (4.8%) were found to have both diagnoses, all were females. In 49.4% of dyspneic adolescents, no diagnosis was found (figure 7). Males were significantly overrepresented among adolescents where no diagnosis was found; 64.7% of males and 38.8% of females remained undiagnosed ($p=0.026$) (figure 8).

Participants with dyspnoea and a diagnosis of EIB and/or EILO where no different from participants with dyspnoea who did not get diagnosed regarding body mass index, lung function ($\text{FEV}_1$), self-reported ever diagnosed asthma or self-reported use of asthma medication (table 5).

| Table 5. Characteristics of subjects with exercise-induced dyspnoea without EIB and EILO versus subjects with exercise-induced dyspnoea with EIB and/or EILO. |
|-------------------------------------------------|-------------------------------------------------|-----------------|
|                                               | Exercise-induced dyspnoea without EIB or EILO | Exercise-induced dyspnoea with EIB and/or EILO | $p$-value     |
| Subjects, n (%)                               | 41 (49.4)                                      | 42 (50.6)       |               |
| Age (years) mean (min, max)                   | 14.29 (13,15)                                  | 14.24 (13,15)   | 0.67          |
| Girls, n (%)                                  | 19 (46.3)                                      | 30 (71.4)       | 0.026         |
| BMI, mean (SD)                                | 20.8 (3.1)                                     | 21.1 (2.2)      | 0.53          |
| $\text{FEV}_1$ % predicted*, mean (SD)         | 91.9 (12.0)                                    | 91.1 (9.5)      | 0.94          |
| Ever asthma, n (%)                            | 16 (39.0)                                      | 19 (45.2)       | 0.66          |
| Inhaled corticosteroids, n (%)                | 7 (17.1)                                       | 12 (28.6)       | 0.30          |
| Short-acting beta agonists, n (%)             | 19 (46.3)                                      | 19 (45.2)       | >0.99         |
| Long-acting beta agonists, n (%)              | 2 (4.9)                                        | 0               | 0.24          |
| Leukotriene receptor antagonists, n (%)       | 2 (4.9)                                        | 3 (7.1)         | >0.99         |
Figure 7. EIB and EILO in adolescents with self-reported exercise-induced dyspnoea. No diagnosis was found in almost half of the tested adolescents.

Figure 8. EIB and EILO in males and females with self-reported exercise-induced dyspnoea. All adolescents with both EIB and EILO were females.
Laryngeal findings during exercise (paper III)

Laryngeal findings assessed with CLE-score

Movements of the laryngeal structures corresponding to a CLE-score 1 at glottic and/or supraglottic level was seen in 74% of controls, in 83% of dyspneic adolescents without a diagnosis and in 66% of adolescents with EIB. Most common in all groups was an isolated supraglottic CLE score 1. The combination of CLE score 1 at both glottic and supraglottic level was more common among controls than in the dyspnoea group (5 vs 1). In subjects with EILO, all but one had supraglottic obstruction only.

Laryngeal findings assessed with EILOMEA

All groups tended to reduce the glottic angle and develop some degree of supraglottic movement that reduced the laryngeal inlet area during increasing work effort. In all three parameters that where investigated, no significant difference could be detected from moderate to maximum effort between controls, the dyspnoea group without a diagnosis of EIB or EILO, and the EIB group. All three parameters differed significantly between subjects diagnosed with EILO compared to the other groups ($p=<0.001$) (table 6).

<table>
<thead>
<tr>
<th></th>
<th>Controls n=28</th>
<th>Dyspnoea, no EIB or EILO n=31</th>
<th>EIB n=10</th>
<th>EILO n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle change (%)</td>
<td>-11.84 (12.56)</td>
<td>-11.46 (12.07)</td>
<td>-13.73 (9.83)</td>
<td>-36.8 (24.24)</td>
</tr>
<tr>
<td>P-factor change (%)</td>
<td>-15.32 (10.41)</td>
<td>-14.89 (11.07)</td>
<td>-9.76 (13.56)</td>
<td>-44.92 (20.73)</td>
</tr>
<tr>
<td>C-factor change (%)</td>
<td>-19.67 (17.46)</td>
<td>-19.93 (17.69)</td>
<td>-17.06 (12.39)</td>
<td>-46.78 (25.37)</td>
</tr>
</tbody>
</table>

Surgical vs conservative treatment for EILO in comparison with patients tested negative (paper IV)

Time between the first questionnaire at diagnostic CLE-test and the follow-up questionnaire was on average 17.6 months. Out of 84 invited subjects, 59 (70%) answered both questionnaires. Results from follow-up questionnaire are presented in table 7.
Impact on exercise-induced dyspnoea

All surgically treated subjects reported less breathing problems when assessed by change in VAS between diagnosis and follow-up. There was a significant difference compared with both conservatively treated subjects and subjects who were tested negative ($p<0.001$).

![Figure 9](image)

*Figure 9.* Change in severity of exercise-induced dyspnoea between diagnostic CLE-test and follow-up as given by visual analogue scores.

Impact on physical activity

Among surgically treated none were less physically active and none had changed sport due to exercise-induced dyspnoea. One third of surgically treated subjects did report a lower physical activity level at follow-up but exercise-induced dyspnoea was not stated to be the cause for this in any of the cases. Instead different sorts of changes in life were mentioned. In contrast, 41.2% of the conservatively treated had adjusted their activity level or started to practice another sport than the sport they practiced at the time for the diagnostic CLE-test. This difference between EILO-groups was found to be statistically significant ($p<0.001$).

Among all EILO positive subjects, surgically treated as well as conservatively treated, practice of endurance sports was more common than practice of interval sports or other sports containing both endurance and interval training. Among subjects tested negative, practice of endurance sport and interval sports were equally common.
Table 7. Data from follow-up questionnaire presenting symptom severity, activity level and practiced sports. All data presented as n (%).

<table>
<thead>
<tr>
<th></th>
<th>EILO ST</th>
<th>EILO CT</th>
<th>Tested negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=14</td>
<td>n=17</td>
<td>n=28</td>
</tr>
<tr>
<td><strong>Symptom severity at follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less symptoms</td>
<td>11 (78.6)</td>
<td>3 (17.6)</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>Symptoms unchanged</td>
<td>3 (21.4)</td>
<td>12 (70.6)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>More symptoms</td>
<td>0</td>
<td>2 (11.8)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td><strong>Activity level at follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less active or adjusted activity because of breathing problems</td>
<td>0</td>
<td>7 (41.2)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Less active, other causes</td>
<td>5 (35.7)</td>
<td>2 (11.8)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>As active as before</td>
<td>5 (35.7)</td>
<td>3 (17.6)</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>More active</td>
<td>4 (28.6)</td>
<td>5 (29.4)</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td><strong>Practiced sports</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance sports</td>
<td>8 (57.1)</td>
<td>10 (58.8)</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Interval sports</td>
<td>2 (14.3)</td>
<td>3 (17.6)</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Other sports</td>
<td>3 (21.4)</td>
<td>2 (11.8)</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Not active</td>
<td>1 (7.1)</td>
<td>2 (11.8)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Changed sport because of breathing problems</td>
<td>0</td>
<td>4 (23.5)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Missing answers</td>
<td>0</td>
<td>0</td>
<td>1 (3.4)</td>
</tr>
</tbody>
</table>
Discussion

The work behind the present thesis aims to increase and deepen the knowledge of exercise-induced dyspnoea with special focus on exercise-induced laryngeal obstruction.

CLE-score vs EILOMEA

In this method comparison study, we investigated if assessments of laryngeal obstructions with EILOMEA (78) were equivalent to assessments made according to CLE-score (3).

Both CLE-score and EILOMEA were developed as diagnostic tools for EILO. CLE-score is the method used in the clinic since it allows evaluation of the dynamic process in the larynx from rest to exhaustion. EILOMEA evaluates measures in a still frame, i.e. a specific moment in this dynamic process. None of the methods can assess all different subtypes of EILO. EILOMEA is highly dependent on a clear view of defined anatomical structures. If supraglottic structures cover the vocal cords, as in CLE-score 3, the glottic values are not possible to obtain. With the CLE-score method it is not possible to score an obstruction where the epiglottis tilts backwards and covers the laryngeal inlet.

Analyses of laryngeal recordings were performed by the two developers of the respective method. By this, user manual misunderstandings as a source of error was avoided, leaving the actual application and technical differences of the methods to account for any lack of correlation. To examine the robustness of the two methods, the raters were given recordings of various subtypes of laryngeal obstructions.

When CLE-score was developed, both patients and healthy controls were tested. Some controls were found to have mild inward movements of laryngeal structures during exercise and thus a CLE-score 1 is not considered to be clinically important. That EILOMEA did not detect differences between CLE-score 0 and 1 for the glottic angle and the supraglottic obstruction is therefore not crucial for a correct medical evaluation.
Prevalence of EIB and EILO

Our findings compared to others

The present cross-sectional study demonstrated that EIB and EILO, assessed using standardized exercise tests, are common in a general population of adolescents. The estimated prevalence of EIB was 19.2% and the estimated prevalence of EILO was 5.7% with no gender differences. In subjects with exercise-induced dyspnoea, EILO alone and EIB in combination with EILO were found to a similar extent. In approximately half of the subjects with exercise-induced dyspnoea, neither EIB nor EILO could be demonstrated and this unexplained self-reported exercise-induced dyspnoea was more common among males than females.

Prevalence numbers for EIB in older children and adolescents ranges between 7-16% in the few previous studies that have been published (24-27). Our prevalence rate was higher, probably due to the use of a strict method (dry air ventilation) and setting the diagnosis at a fall in FEV₁ ≥ 10%.

Comparing results in EILO studies are even more difficult since study populations, methods and diagnostic criteria vary (35, 73, 97). Additionally, many different terms have been used which adds further confusion (5, 15, 113) and no difference is made between inducers; exercise-induced laryngeal obstruction is often not considered to be any different from laryngeal obstructions induced by other triggers.

There is only one previous study that have investigated the prevalence of EILO in a general population (33). EILO was found in 7.6% in a population with mean age 18.6 years. Dropouts during this previous study was very high, only 17.6% of participants entering the study performed a CLE-test. In our study 83.3% of adolescents entering the study completed both an EIB and a CLE-test and mean age was 14.2 years.

Gender differences

No gender differences were found neither for EIB nor EILO. For EIB this is consistent with results from other studies (114, 115). However, there are studies who do report gender differences for EIB (24, 27) and interestingly the prevalence is higher in females. Females are also overrepresented in most studies and case reports on EILO (33, 38, 113, 116). The main difference between our study and other studies was that participants in the studies where a gender difference was found were older. This might indicate that gender difference depends on larynx size. The size of the laryngeal opening does not differ between males and females in pre-pubertal age. During puberty, the larynx grows more in males than in females and it has reached adult size by the age of 16-17 years (117, 118). In our study, CLE-tests were conducted during a period of 1.5 years and some of the participants were still pre-pubertal when
tested. We found four males with supraglottic EILO, all of them born in 1998, and three of them born at the end of the year, thus being among the youngest participants in the study. All males with EILO, as a group, were younger than the females, mean age being 14.2 and 15.0 respectively.

Can we trust the prevalence numbers?

The estimated prevalence of EIB was 19.2% and the estimated prevalence of EILO was 5.7%. Since study II was an extension of a previous survey investigating the prevalence of exercise-induced dyspnoea (19), it is necessary to take the methodology and results from that survey into account when we interpret the prevalence results.

The survey was sent to adolescents born in 1997-1998, who at the time were 12-13 years old. The prevalence of exercise-induced dyspnoea in this study was 14.3%. Exercise tests in study II started approximately one year later and went on for 1.5 years, meaning that the oldest tested adolescent was 15 years old. Mean age in the total tested population was 14.2 years.

The response rate to the survey was 60.2%. No differences were seen among responders and non-responders regarding age, gender or postal code. Although the response rate is acceptable, there is a risk of overrepresentation of adolescents that experience exercise-induced dyspnoea.

The survey contained over 30 questions comprising questions about exercise-induced dyspnoea, asthma, allergy and physical activity. We used the question “Have you had an attack of shortness of breath that happened after strenuous activity at any time during the last 12 months?” (111) as a screening question for exercise-induced dyspnoea. This question has been proven to be useful in detecting asthma (119) but have not been tested for other diagnoses. The wording “…after strenuous exercise” might have played a role. In EIB, symptoms typically occur after exercise but EILO symptoms typically occur during the exercise. If the question was interpreted literally, adolescents that experienced dyspnoea during exercise might not have answered affirmative to this particular question, and wrongly been classified as a control in study II. Our intent with the question, however, was the opposite: we wanted adolescents not only with typical asthma to answer yes to this question. This is also more likely to be the case since 67% of adolescents who reported exercise-induced dyspnoea had no asthma diagnosis. It is possible that we got affirmative answers from adolescents with poor physical condition, which might be an explanation for the high proportion of adolescents reporting dyspnoea who remained undiagnosed. Poor physical condition has been confirmed to be common in retrospective studies investigating the accuracy of an earlier asthma diagnosis (21, 22, 120). As exclusion criteria for the study, we asked about heart conditions and lung conditions apart from asthma, but we did not investigate any other diagnoses that can cause exercise-induced dyspnoea.
Recall bias must always be taken into consideration (121). Also, this questionnaire was not validated as an entity but many of the questions had previously been used in other population studies.

Factors in study II that might have influenced the prevalence numbers

There is a possibility of a selection bias in the process where adolescents accepted to enter study II. People with a disease or symptom tend to be more prone to participate in studies about this particular condition. The survey preceding study II included a question about “ever being diagnosed by a physician as having asthma”. Both among adolescents reporting exercise-induced dyspnoea and among controls there were more adolescents who had answered yes to this question and chose to participate, than among adolescents who declined participation. This, however, does not confirm for certain that they had asthma. Since EILO can be mistaken for asthma, some of the adolescents with an asthma diagnosis could in fact have EILO instead.

_EIB-test_

All adolescents were tested for EIB in the same way following a standardized protocol and recommended guidelines (32). The investigator was blinded to whether the test subject had stated exercise-induced dyspnoea or not and could not influence the test result. The subjects breathed dry air with a nose clip during the EIB-test. This has not been done in other studies (24, 25, 27, 28), and might have increased the sensitivity of the test, thereby increasing the prevalence. The sensitivity of the test might also have been increased by ensuring high effort exercise throughout the test (64).

Guidelines for the EIB-test includes instructions for the person to be tested. The adolescents were instructed to cease asthma medications before the test but if that was followed by everybody is uncertain. If effect of asthma medication were present at the time of the test this may have led to false negative results.

Spirometry was performed several times. Reliable results depend on a motivated patient performing the procedure correctly. In this study, the investigator instructed all adolescents in the same way and made certain that the test subject had a correct technique. It is possible that symptoms can be affected by other factors and vary over time, especially if the adolescent also have asthma. It would therefore have been interesting to test the adolescents twice, even if the EIB-test has been shown to be reproducible in the majority of subjects tested in a study by Anderson et al (122).
**CLE-test**

All adolescents were tested for EILO in the same way following a standardized protocol which was a modified version of the CLE-test (1). Electrocardiogram or oxygen uptake was not measured during the test, only heart rate, but this has been reported to be sufficient (108). All tested adolescents reached 90% of predicted maximum heart rate. The investigator was blinded to whether the test subject belonged to the dyspnoea group or the control group, and to the result of the EIB-test. The investigator could not influence the test result.

Performing laryngoscopy continuously during exercise is gold standard for investigating EILO but the test has some weaknesses. For the test to be successful the test subject must reach maximum exercise capacity. If the person stops too early symptoms might not be triggered. The result is therefore highly dependent on the motivation and expectations of the subject tested, and he or she must feel safe in the test situation. For a person with EILO it can be very stressful to expose themselves to a situation where breathing problems might occur. Thus, this anticipating anxiety can hinder the person from trying their best which might lead to a false negative test result.

The CLE-test is performed on treadmill in a laboratory setting which cannot be compared with situations during exercise in “real life”, like a stressful competitive situation for the athlete. This can also have influenced the prevalence numbers. Also with the CLE-test it would have been desirable to test the adolescents twice. No studies have yet examined the reproducibility of the CLE-test.

Before the fibre-optic laryngoscope was inserted, naphazoline-lidocaine was sprayed twice into each nostril to achieve local anaesthesia and dilatation in the nasal cavity. A small amount of the anaesthetics is transported to the laryngopharynx. There are no studies on how, or if, local anaesthetics applied in this way affect the laryngeal reflexes, and more specifically, the glottic closure reflex. If the aetiology for glottic EILO is in fact an impaired neurological function, then locally administered anaesthetics could have reduced the prevalence numbers for glottic EILO in our study. However, if aetiology for glottic EILO are caused by aerodynamic forces acting on laryngeal tissue, this is less likely, even though the hyperventilation itself can trigger a glottic response (81, 86). In the clinic, we have seen two types of glottic obstruction. One where the vocal cords adduct abruptly or gradually during the exercise session, and one where the glottis closes like a zipper, starting in the anterior commissure. The latter might be caused by aerodynamic forces. In study II we found one adolescent with glottic EILO (adduction type), the remaining ten had supraglottic EILO.
**CLE-scoring**

CLE-score allows assessment of obstructions at glottic and supraglottic level on an ordinal scale graded 0-3. A higher number means more severe obstruction. The CLE-score method has been shown to correlate well with the symptoms as reported by patients and assessed by observers (3). EILO is defined as a CLE-score 2 or more *in conjunction* with exercise-induced dyspnoea. In the present study, we observed two adolescents in the control group, one male and one female, with supraglottic obstruction grade 2. Even though they had obvious supraglottic obstructions, both stated exhaustion and not dyspnoea as the reason for them to stop running on the treadmill.

The normal laryngeal response to exercise is not completely known, i.e. we don’t know exactly what findings should be considered normal and what should be considered pathological. To put up criteria that differs healthy subjects from subjects with EILO is difficult. Mc Fadden et al proposed that vocal cord adduction exceeding 50% should be regarded as consistent with vocal cord dysfunction (42), but if, and when, a person experiences dyspnoea is subjective. Many other factors contribute to whether a subject will be diagnosed with the “disease” EILO (symptomatic EILO), or diagnosed with the “laryngeal finding” EILO (asymptomatic EILO). The size of the laryngeal inlet at rest compared to at a high workload, body size, physical condition, motivation and other psychological factors can all influence the laryngeal response we observe. The motivation to exercise hard was very strong in the healthy subject with supraglottic obstruction grade 2 in our study. One might speculate if the supraglottic obstruction in these asymptomatic EILO subjects is an effect on the laryngeal structures of high intensity exercise, and that the laryngeal obstruction occurs in symptomatic EILO subjects before they had the chance to exercise as hard as they wanted.

The scoring we did in this study resulted in eleven EILO positive adolescents and from this a prevalence of 5.7% in the general population was estimated. However, this prevalence number is in fact not the prevalence of symptomatic EILO, but the prevalence of both symptomatic and asymptomatic EILO, i.e. the prevalence of laryngeal findings consistent with an EILO diagnosis. Thus, the CLE-score as a diagnostic tool for EILO not always diagnose the actual condition that causes exercise-induced dyspnoea. Regardless, symptomatic EILO is not uncommon and should be diagnosed and treated.

**Dropouts**

A total of 25 participants did not complete both exercise tests. However, as a group these adolescents did not differ from the adolescents who completed both tests regarding baseline characteristics. It is therefore unlikely that these dropouts have affected the prevalence estimate of EILO.
Larynx during exercise in adolescents with and without dyspnoea

Consensus in the literature is that the larynx is maximally opened during exercise to facilitate airflow. Just before exhaustion, at maximum minute ventilation, a discrete adduction of the arypepiglottic folds can be noted (4, 15, 62). EILOMEA analyses showed that all adolescents tended to reduce the glottic angle and develop some degree of supraglottic obstruction during maximum exercise. Additionally, we found that we tended to underestimate the glottic obstruction when we used the CLE-score.

The pattern of mild obstruction at both glottic and supraglottic level was seen in five of the controls, but only in one of the adolescents with exercise-induced dyspnoea. This indicates that the additive effect of mild obstruction at two levels is not clinically important, at least not if no feeling of respiratory distress is present.

The typical dynamic development described for EILO is that the supraglottic adduction occurs first and the glottic involvement follows (4, 33). One might speculate if the controls could work harder for a longer time so that the glottic engagement was starting to emerge before they finally stopped exercising. Among adolescents with EILO the majority had supraglottic obstruction grade 2 but the span of what we have assessed as a grade 2 is rather wide. This highlights the difficulties of the CLE-score being assessed on an ordinal grading scale. A grade 1 or 3 is more clearly defined than a grade 2 which might lead to that a wider range of obstruction severity will be assessed as grade 2.

Only one adolescent had glottic obstruction only. When analysing the results, we included this adolescent in the total group of EILO subjects. This might have increased the difference seen between EILO subjects and the other groups regarding the glottic angle and area. In EIB, expiratory glottic obstruction has been described (55, 67). In the present study, we only present measurements on glottic angle and area during inhalation at the same time as the maximum supraglottic obstruction occurred. We therefore do not know if the EIB-group, or other groups, kept the vocal cords adducted also during exhalation. The fact that we performed within subject comparison and adjusted for the values obtained at moderate effort, minimizes the impact of individual larynx size.

Surgical vs conservative treatment

This follow-up study investigated the outcome of supraglottic surgery for EILO compared to the outcome of conservatively treated EILO. Additionally, the study included the patients tested for EILO but who did not get an EILO-diagnosis. Questionnaires were sent to all patients that, at that time, had been
tested on treadmill at our clinic (n=84). Conservative treatment implies breathing exercises (treatment for all EILO subtypes), and speech therapy (treatment for glottic EILO). Conservatively treated patients in this study with the supraglottic subtype did, however, not follow a structured treatment program, which means that they can be regarded as untreated.

Prior to the present study, only one follow-up study had been published in which both surgically and conservatively treated EILO patients were investigated (38). Our questionnaires were similar but none of them validated. As earlier discussed (paper II), many types of biases can affect the results when a questionnaire is used and one important bias is recall bias. We also have a selection bias since the response rate was considerably higher in surgically treated than in conservatively treated (93% vs 53%).

Based on self-reported information, surgically treated EILO patients had less exercise-induced dyspnoea, were more physically active and had not to the same extent as the other groups adjusted their physical activity level by changing what sport they practiced. It would have been interesting to have re-tested all surgically treated patients to obtain objective data. As a routine, all operated patients are invited to perform a second CLE-test six months after the operation but too few in this study had performed such a test.

Potential biases in terms of positive and negative expectations must be taken into consideration. Surgically treated might be grateful for having something done at all and overestimates the effect. On the other hand, if their expectations are too high, they will be disappointed even if they manage to perform better on a CLE-test after surgery. Conservatively treated might be disappointed over having an inoperable subtype of EILO. All these biases may have influenced the results.

Who should be offered surgical treatment?
The decision to operate must be taken on a solid ground. Surgery can be considered when severe supraglottic EILO is seen in combination with a strong subjective sensation of dyspnoea in a motivated patient with expectations on a realistic level. Additionally, surgery should preferably be offered only to adolescents and adults where the larynx has reached adult size.

Future perspectives on EILO
Our prevalence study in adolescents shows that EILO is not an uncommon diagnosis. Despite progress in recent years, EILO is unfortunately too often misdiagnosed as exercise-induced asthma or EIB. We need to increase the awareness of EILO in the medical field so that persons with symptomatic EILO are diagnosed correctly and can be offered adequate treatment.
EILO is most likely not a single disease with a single cause. We need to learn more about aetiology and pathophysiology, and try to identify the factors that underlie why some persons present with exercise-induced symptoms when other do not, even though they have similar obstructions in the larynx. By developing better diagnostic methods which can be used in a more “real-life”-exercise situation, we can learn a lot. We must also conduct randomized controlled trials where we investigate the impact of co-morbidities and objectively evaluate the effect of treatment. We also need to develop guidelines for treatment of the different subtypes of EILO. The terminology recently suggested by a Task force needs to be implemented in both clinical practice and in research.
Conclusion

In this thesis, we have investigated the prevalence of EIB and EILO in a general population of adolescents with two separate, standardized exercise-tests. Main findings are that EIB and EILO are important diagnoses in adolescents with exercise-induced dyspnoea. EILO is not uncommon and should be investigated early in the diagnostic process if EIB and asthma is not diagnosed or if medical therapy, despite a diagnosis, does not provide symptom relief. We also confirmed that EIB and EILO can coexist.

For EILO the investigation was conducted according to gold standard with CLE-test and the use of CLE-score as diagnostic tool. By comparing CLE-score and EILOMEA we found the methods compatible. EILOMEA offers a possibility to study laryngeal differences and changes in detail. By use of these two validated methods we could further establish that there were no differences in laryngeal findings between healthy controls and adolescents that remained undiagnosed after EIB-and CLE-tests. Only adolescents with EILO differed from other participants regarding glottic and supraglottic measurements obtained with EILOMEA. This strengthens the use of current diagnostic procedures as it indicates that, when typical laryngeal findings are seen during exercise in a person with dyspnoea, and who recognizes these symptoms as their main problem, we diagnose EILO correctly.

A correct diagnosis of EILO is mandatory when it comes to offering treatment to EILO-patients. Surgical treatment should exclusively be offered to highly motivated patients with severe supraglottic EILO, where the diagnosis has been established during a CLE-test. Surgically treated patients in our study reported reduced exercise-induced dyspnoea and a positive effect on physical activity levels.
Populärvetenskaplig sammanfattning


För att ta reda på om någon har EILO måste struphuvudet undersökas samtidigt som personen anstränger sig kraftigt. Om man undersöker struphuvudet i vila ser allt normalt ut. Utan en korrekt undersökning kan EILO lätt misstas för att vara ansträngningsastma och det är vanligt att personer med EILO har behandlats med astmamedicinering utan att det haft någon effekt. Vid undersökning förs en tunn fiberoptisk kikare in via näsan så att spetsen på kikaren kan placeras strax ovanför struphuvudet. Den fiberoptiska kikaren är kopplad till en kamera så att det går att följa vad som händer i struphuvudet medan personen som testas springer på ett löpband (på foto s. 21 kan man se ungefär hur långt ner kikaren når eftersom ljuset från kikaren syns på halsen).

I det första arbetet jämfördes två olika metoder som kan användas för att diagnostisera EILO. Den ena metoden (CLE-score) används i samband med att ansträngningstestet görs och innebär att man graderar hur kraftigt förträngningen som uppstår i struphuvudet på en skala från 0-3. Den andra metoden (EILOMEA) innebär att man tittar på en filminspelning av vad som hänt i struphuvudet, tar ut en bild från filmen som visar den maximala förträngningen som uppstått vid inandning och sedan, med hjälp av ett dataprogram, räknar ut hur kraftig förträngningen är. Vid jämförelse av metoderna fann vi att bedömningar med EILOMEA och CLE-score överensstämde för de förträngningar i struphuvudet som kan ha klinisk betydelse.

Det tredje arbetet var en fortsättning på den föregående studien. Det var inte alla som hade uppgett ansträngningsutlösta besvär som fick någon av de diagnoser vi undersökte. Vi undrade då om förklaringen till deras upplevda andningsbesvär ändå kunde vara relaterad till struphuvudet. Genom att undersöka filmerna som spelats in under ansträngningstesterna togs stillbilder ut från början och slutet av testet och undersöktes med EILOMEA. Vi kunde då mäta hur mycket trängre det hade blivit i struphuvudet under tiden som de ansträngt sig. Vi kunde inte hitta någon skillnad mellan de som hade angett besvär och de friska kontrollerna och drog slutsatsen att orsaken till de upplevda andningsbesvären inte sitter i struphuvudet.

Om ansträngningen ger upphov till en kraftig förträngning på grund av att sleminnevecken lägger sig framför ingången till luftstrupen så kan dessa veck minskas ner genom operation. I det fjärde arbetet gjorde vi en enkätundersökning där vi ställde frågor till patienter som tidigare remitterats till vår klinik för utredning av andningsbesvär under ansträngning. Vi jämförde svarren vi fick med de svar som patienterna angett då de genomförde ansträngningstestet. Vi var intresserade av att se hur de som opererats mådde jämfört med de som inte opererats. Undersökningen visade att de som opererats hade mindre andningsbesvär och att de kunde anstränga sig mer än tidigare. De som inte hade opererats uppgav till stor del oförändrade besvär och många hade försökt anpassa sig till besvären genom att hitta andra former att träna än de gjort tidigare. Resultaten tyder på att operation är effektivt hos de som har en kraftig förträngning i struphuvudet och att det är viktigt att göra en noggrann undersökning så att rätt patienter får rätt behandling.
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