Exercise - Induced Laryngeal Obstruction

Diagnostic procedures and therapy

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Abbreviations

AEF	Aryepiglottic fold
CLE-test	Continuous laryngoscopy exercise test
EIA	Exercise-induced asthma
EIL	Exercise-induced laryngomalacia
EILD	Exercise-induced laryngeal dysfunction
EIIS	Exercise-induced inspiratory stridor
EILO	Exercise-induced laryngeal obstruction
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
LAR	Laryngeal adductor reflex
LM	Laryngomalacia
LPR	Laryngopharyngeal reflux
NSD	Norsk samfunnsvitenskapelig datatjeneste
PVFM	Paradoxical vocal fold motion
PFMD	Paradoxical vocal fold motion disorder
RFS	Reflux finding score
SD	Standard deviation
TFL	Transnasal fiberoptic laryngoscopy
VAS	Visual analogue scale
VCD	Vocal cord dysfunction
VFMD	Vocal fold mobility disorder

Contents

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Abstract

Introduction: Exercise-induced inspiratory stridor (EIIS) is not uncommon in adolescents. It can be caused by airflow obstruction at different levels of the airways but most often at the laryngeal level. Although the larynx may function perfectly normally during quiet breathing, obstruction of airflow through the larynx can cause respiratory distress and stridor during exercise. In the literature, there is confusion over the terminology used for this phenomenon. One of the more recent terms, exercise-induced laryngeal obstruction (EILO) has the advantage that previous terms can be included into its framework. Laryngeal obstruction typically induces inspiratory stridor as opposed to asthma causing expiratory wheeze. Still, these conditions are all too often mixed up, and maltreatment can be a consequence. In order to ease the differentiation between these conditions, a setup for continuous laryngoscopy during exercise had been established prior to the commencement of this work (Heimdal et al., 2006).

Aims: The first aim of this thesis was to apply the continuous laryngoscopy exercise (CLE)-test on a larger series of patients experiencing exercise-induced inspiratory stridor (EIIS). Clinical application of the test uncovered a need for a more objective evaluation of findings, and therefore the second aim was to develop a scoring scheme that could be used to grade the level and severity of laryngeal obstruction and to assess the reliability and validity of this CLE-test score.

We experienced that some patients had serious problems with respiratory distress during exercise and therefore we offered surgical treatment to patients selected by clinical criteria; i.e. if the patients experienced severe distress during exercise, were highly motivated for surgical treatment in order to reduce symptoms, and we could observe a severe obstruction of the laryngeal inlet during the CLE-test. The third aim was therefore to use the CLE-test in order to reveal the effect of surgical treatment on the laryngeal motion and symptoms.

As most EILO patients are teenagers, one could hypothesise that a natural development and enlargement of the larynx during growth would reduce the laryngeal obstruction during exercise. The fourth aim of this thesis was therefore to assess the natural course of EILO and to assess the long term effect of surgical treatment of supraglottic EILO.

Methods: The CLE-test was performed according to the description by Heimdal and co-workers (2006). Video and sound recordings were edited into new data files and could thereby be reviewed in a random order without any clinical information in order to secure a best possible objective assessment. Additional information about symptoms was revealed by questionnaires and visual analogue scores (VAS). In the follow-up study, change in symptoms of exercise-induced breathing distress, level of activity, and the impact of symptoms on daily life activity was addressed in questionnaires sent by mail. All surgically treated patients and selected patients from the initial part of study were invited to perform a second CLE-test.

Results: In the first study, the CLE-test turned out to be feasible in order to reveal level and severity of laryngeal obstruction in EILO patients. We observed that the larynx could be obstructed only at the supraglottic level but most often in combination with obstruction also at the glottic level. The latter was rarely found to be the sole cause of EIIS.

When CLE-scores of laryngeal obstruction were evaluated in the second study, inter- and intra-observer agreement was moderate to very good. The test was found to be interpretable and also valid as scores were significantly correlated with the severity of respiratory distress symptoms when assessed both by the patients and by observers.

The third study included 10 patients for surgery according to the clinical criteria. The patients reported a better ability to breathe while exercising, after surgical treatment, as revealed by VAS scores. Postoperatively, the CLE-test showed an increased abduction of the supraglottic structures during both moderate and maximal exercise.

The fourth study included; re-examination of 14 patients, initially tested when teenagers, with a second CLE-test at adult age; a re-examination of 19 of 24 surgically treated patients and; follow-up concerning symptoms of 73 of the 94 patients invited to the study. This study showed that most subjects experienced symptom relief during the observation time, but more so in the surgically treated than untreated patients. Comparison of 19 pre- and postoperative CLE-tests showed a significant improvement in the ability to keep the larynx open, while exercising, in the surgically treated group. On the contrary, little change was observed in laryngeal motion in 14 re-tested, untreated patients.

Concluding remarks: We conclude that exercise-induced laryngeal obstruction can be visualized by the CLE-test and that the obstruction of the larynx in EILO patients is most often due to an inward rotation of the aryepiglottic folds, frequently followed by a narrowing of the glottic space, and seldom solely due to glottic adduction. In some cases, major distress and panic reactions can be the endpoint of this phenomenon. The severity of obstruction can be graded by the CLE-score in a reliable and valid manner. Surgery of exercise-induced laryngeal obstruction can be an adequate treatment in strictly selected cases, depending of severity of symptoms, degree of obstruction, and motivation of the patient. EIIS due to EILO does not seem to recover spontaneously in youngsters. Reduced physical activity may give the impression that the laryngeal function has improved.

1. Introduction

1.1 Exercise-induced laryngeal obstruction

Exercise-induced inspiratory stridor (EIIS); respiratory distress with a high-pitched inspiratory noise, shortness of breath, and occasionally, panic reactions, in often-active youngsters, has been a diagnostic challenge for decades (Rundell and Spiering, 2003). EIIS typically occurs during vigorous exercise and spontaneously resolves within a few minutes after exercise termination. EIIS can be caused by a variety of conditions, e.g. anatomical malformations of the larynx and trachea or vocal fold immobility but, in most cases an examination of the airways at rest reveals no pathological conditions. In such cases, where the upper airway flow-limitations are induced only by exercise, a continuous laryngoscopy, during exercise, often demonstrates an inward collapse of supraglottic structures, in some cases simultaneously with adduction of the vocal folds and in rare cases, with adduction of the vocal folds only (Bent et al., 1996; Bjornsdottir et al., 2000; Tervonen et al., 2009; Tilles and Inglis, 2009). The larynx represents the portion of the upper airways where the resistance to airflow is most variable and reduction of the laryngeal inner lumen increases the resistance to airflow and probably induces airflow turbulence. This airway obstruction may cause extreme dyspnea and audible wheeze or stridor (Bjornsdottir et al., 2000; Lakin et al., 1984).

Lack of familiarity with this specific diagnosis, as well as lack of diagnostic tools, has the consequence that a considerable number of physically active youngsters with laryngeal obstruction have been misdiagnosed and incorrectly treated for asthma or accused of malingering. Although the use of flexible endoscopes has facilitated a more adequate examination of the laryngeal motion during exercise, there still is much to be addressed concerning adequate use of terminology, prevalence, aetiology, (patho-) physiology, effects of treatment and prognosis of exercise-induced airway obstruction at the laryngeal level.

1.2 Historical aspects

Laryngeal obstruction causing respiratory distress was first described by Dunglison in a medical textbook in 1842. He described a disorder of the laryngeal muscles brought on by 'hysteria' (Dunglison, 1842). In 1869, MacKenzie visualized, paradoxically, closure of the glottis during inspiration in hysteric adults with stridor (MacKenzie, 1869). Later, in 1902, William Olser defined this condition by describing patients with 'spasms of laryngeal muscles' occurring during inspiration and times of great distress (Olser, 1902).

Until the 1970's, little was published on this topic and the condition was described mainly in psychiatric literature. Psychogenic factors have been associated in a majority of case reports and clinical studies. A case report entitled 'Munchausen Stridor' in 1974 illustrated attacks with inspiratory wheeze, worsened by infection or emotional distress (Patterson et al., 1974).

During the 1980's, episodic obstruction of the larynx became recognised as a clinical entity with the appearance of an increasing number of publications on this topic. Hereafter, this condition has been more often described in journals of otolaryngology and respiratory medicine as a syndrome of episodic stridor, dyspnea and palpitations that mimics, or is mistaken for, asthma or malingering. The fact that laryngeal obstruction can be induced by exercise has also received more focus (Abu-Hasan et al., 2005; Christopher et al., 1983; Kayani and Shannon, 1998; Kenn, 2007; Landwehr et al., 1996; McFadden and Zawadski, 1996; Morris et al., 1999).

In most of the early reports the focus was on laryngeal obstruction at the glottic level i.e. inappropriate adduction of the vocal folds. Christopher and co-workers were the first to describe obstruction due to adduction of the false vocal folds simultaneously with adduction of the true vocal folds (Christopher et al., 1983).

The first paper describing a solely supraglottic cause of laryngeal obstruction during exercise was published by Lakin (Lakin et al., 1984). He described the phenomenon as a separate entity and found an inspiratory prolapse of the corniculate and cuneiform cartilages in the posteroinferior portion of the aryepiglottic folds over the laryngeal vestibule, narrowing the supraglottic aperture, while the vocal folds where widely abducted. Later, similar results were described by several other authors (Bent et al., 1996; Bittleman et al., 1994; Bjornsdottir et al., 2000; Chemery et al., 2002; Fahey et al., 2005; Mandell and Arjmand, 2003; Smith et al., 1995).

1.3 Nomenclature confusion

Since the first description by Dunglison, up until the present time, different terms have been used to describe the phenomenon of laryngeal obstruction causing respiratory distress. These terms are related to the hypotheses and available diagnostic tools, or lack of such, at the actual time. The use of mirror laryngoscopy initially enabled the investigators to examine the larynx only during quiet breathing, and only pathological motion patterns of the larynx present during rest could be described. One had to deduce findings during rest into the situation of exercise.

In the last three decades, the introduction of flexible laryngoscopes has made it possible to examine the larynx when patients experience symptoms during exercise. Such studies have revealed that obstruction of the larynx is complex and occurs at different levels. The observation of obstruction of supraglottic structures, simultaneously with an adduction of the vocal folds, or a solely supraglottic cause of laryngeal obstruction, has led to further discussion as to how this phenomenon should be termed.

The findings of supraglottic collapse similar to that observed in newborns with laryngomalacia has led to the introduction of terms to the nomenclature that imply a connection between laryngomalacia and exercise-induced laryngeal obstruction, e.g. the term *exercise-induced laryngomalacia* introduced by Bent and co-workers and later used by others (Bent et al., 1996; Chemery et al., 2002; Mandell and Arjmand, 2003; Smith et al., 1995), or similarly; *adult laryngomalacia* by Gessler and co-workers (Gessler et al., 2002).

The most often used term to describe airway obstruction at the laryngeal level is exercise-induced vocal cord dysfunction (EIVCD), indicating that the obstruction is solely present at the glottic level (Brugman, 2003; Davis et al., 2007). In most publications the prefix *exercise* is erased and only VCD is used although the trigger might in fact be exercise (Morris and Christopher, 2010). Consequently the term VCD is used on a broad spectrum of (non-) organic disorders involving the larynx and/or periglottic structures, causing confusion as to which pathology or pathophysiology has been found in each case. VCD does not differentiate inspiratory from expiratory vocal fold adduction and has been applied to an excessive-expanding array of clinical presentations (Christopher, 2006).

More than 85 terms have been used in literature in order to describe respiratory distress caused by airway obstruction at the laryngeal level; Table I illustrates an overview. This fact indicates that there is no clear understanding as to the pathophysiological mechanisms of EILO. This is not a new matter; uniformity in assessment of clinical diagnosis of laryngeal pathology has been discussed before (Dikkers and Schutte, 1991). In 2010, the issue of terminology confusion of exercise-induced pathology has been discussed in the European Laryngological Society (ELS) and the European Respiratory Society (ERS) and a joint ELS/ERS Task Force was established to develop common guidelines for nomenclature.

TABLE I

Terminology used to describe causes of respiratory distress, originating at the laryngeal level

Adductor breathing dystonia

Adult spasmodic croup

Acquired laryngomalacia

Adult laryngomalacia

Asthma-like disorder

Asthmatic extra-thoracic upper airway obstruction

Atypical asthma

Benign paradoxical vocal cord motion

Bilateral abductor vocal cord paresis

Emotional laryngeal wheezing

Emotional laryngospasm

Episodic laryngeal dysfunction

Episodic laryngeal dyskinesia

Episodic laryngospasm

Episodic paroxysmal laryngospasm

Exercise-induced laryngomalacia

Exercise-induced laryngospasm of emotional origin

Exercise-induced laryngochalasia

Exercise-induced laryngeal prolapse

Exercise-induced supraglottic closure

Exercise-induced (paradoxical) vocal cord dysfunction

Exercise-related laryngomalacia

Expiratory laryngeal stridor

Extra-thoracic airway dysfunction

Factitious asthma

False croup

Familial Munchausen stridor

Factitious asthma

Functional abduction paresis

Functional asthma

Functional breathing disorder

Functional laryngeal dyskinesia

Functional laryngeal obstruction

Functional laryngeal stridor

Functional (inspiratory) stridor

Functional upper airway obstruction

Functional vocal cord paralysis

Glottic dysfunction

Hysteric croup

Hysterical stridor

Inspiratory vocal cord dysfunction

Intermittent arytenoid region prolapse

Irritable larynx syndrome

Irritant-associated vocal cord dysfunction

Laryngeal asthma

Laryngeal dysfunction

Laryngeal dyskinesia

Laryngeal respiratory dystonia

Laryngeal spasm

Laryngeal stridor

Laryngismus fugax

Laryngismus stridulous

Laryngoneurosis

Late-onset laryngomalacia

Munchausen syndrome presenting as bronchospasm

Munchausen stridor	Psychosomatic stridor
Nonorganic stridor	Psychosomatic wheezing
Nonorganic upper airway obstruction	Respiratory glottic spasm
Paradoxical vocal cord adduction	Reversible upper airway obstruction
Paradoxical vocal cord dysfunction	Sleep-related laryngospasm
Paradoxical vocal cord motion	Spasmodic croup
Paradoxical vocal cord movement	Spasmodic croup in the adult
Paradoxical vocal fold dysfunction	Stress-inducible functional laryngospasm
Paradoxical vocal fold motion	Suffocative laryngismus
Paroxysmal laryngospasm	Thymic asthma
Pseudo-asthma	Upper airway dysfunction syndrome
Pseudo-steroid-resistant asthma	Upper airway obstruction misdiagnosed as asthma
Psychogenic laryngeal dysfunction	Variable extra-thoracic obstruction
Psychogenic respiratory distress	Variable vocal cord dysfunction
Psychogenic stridor	Vocal cord dysfunction masquerading as asthma
Psychogenic stridor caused by a conversion disorder	Vocal cord dyskinesia
Psychogenic upper airway obstruction	Vocal cord malfunction
Psychogenic vocal cord dysfumction	

Modified after Brugman; *What's this thing called Vocal Cord Dysfunction? (Brugman, 2003)*

1.4 Definition of the term EILO

Whilst overwhelming in number, none of the available terms actually strictly differentiate symptoms from objective laryngeal findings, or physiological triggers from pathological conditions (Brugman, 2003). There is therefore, a need for a term that takes into consideration the aspects mentioned by Brugman. Such a terminology has not previously been available but EILO has been suggested as a term that covers several of the aforementioned and used, terms (Christensen et al., 2011).

The term EILO will, in this thesis, be defined as airway obstruction visualized at the laryngeal level by continuous laryngoscopy during exercise in patients with EIIS-symptoms if their larynx is functioning normally at rest.

EILO will be separated according to the level of obstruction in the larynx, i.e. supraglottic if the obstruction is dominant above the vocal folds, or glottic if the obstruction is dominant at the glottic level. If both levels are involved the term “combined type of EILO” will be used.

1.5 Magnitude of the EILO problem

The overall incidence of EILO in a general population has not yet been defined. The magnitude of the EILO problem has been addressed in recent studies in different ways and the estimates therefore vary. Christensen and co-workers invited 556 youths in Copenhagen to perform an exercise test with continuous laryngoscopy recordings. They concluded that 7.5% of the invited subjects had EILO (Christensen et al., 2011). Kenn and co-workers performed a study including 1025 patients with dyspnea and reported an overall incidence of 2.8% (Kenn, Willer et al. 1997). A study including military patients with exertional dyspnea by Morris and co-workers, revealed that 15% of the studied subjects had some degree of adduction of the vocal folds during exercise (Morris et al., 1999). There are observations indicating that females are more prone to have EILO than males (Bjornsdottir et al., 2000; Christopher and Morris, 2010 ; Smith et al., 1995). Based on the available studies so far, only crude estimates concerning the magnitude of the EILO problem can be put forward until population based studies are performed.

1.6 Differential diagnoses to EILO

EILO versus EIA

Although EILO has been recognized as the most common cause for EIIS, the symptoms of EILO are still often confused with those of exercise-induced asthma (EIA) and therefore the EILO condition can be misdiagnosed as EIA (Carlsen, 2011; Morris et al., 2002). However, EILO even coexists with EIA (Morris et al., 1999; Rundell and Spiering, 2003).

There are certain differences between the conditions that should ease the differentiation between them: Patients with EIA can usually undertake and finish vigorous activity, but the acquired airway obstruction begins shortly *after* the termination of exercise, reaches its peak in 5-10 minutes, and then remits spontaneously (McFadden and Gilbert, 1994). In contrast, in patients suffering from EILO, the acquired airway obstruction begins and peaks during exercise.

Exercise-induced asthma (EIA) is defined by lower airway obstruction causing symptoms of coughing, wheezing, or dyspnea induced by exercise in patients with underlying asthma (Schwartz et al., 2008). Symptoms may be wheezing (mostly expiratory), dyspnea, coughing and chest tightness.

EIA can be confirmed by demonstrating decreased values for expiratory flow rates and forced expiratory volume in the first second (FEV_1) when performing spirometry after an exercise challenge (Carlsen and Carlsen, 2002; Rice et al., 1985). EIA is considered the aetiology for exercise-induced dyspnea (EID) if the treadmill exercise results in reproduction of symptoms in association with a decrease in FEV_1 of at least 15% (Abu-Hasan et al., 2005).

Respiratory sounds can be a help when the level of airway obstruction is to be determined. Stridor or wheeze is heard mostly during inspiration in EILO whereas in EIA the stridor or wheeze is mainly apparent during expiration.

Stridor is a harsh, high pitched, musical sound, which can be produced by turbulent airflow through a partially obstructed airway, explained by the Venturi principle (Forgacs, 1978). It is often referred to as an inspiratory sound that is loudest over the central airways (Wilkins et al., 1990). Stridor is not a diagnosis but a symptom of underlying pathology. It can be created by both dynamic and solid obstruction in any part of the airway, though it originates mostly from obstruction in the laryngeal and tracheal part (Bent, 2006). *Two-way stridor* is usually associated with a more severe degree of obstruction, in contrast to the loudness of the stridor, which does not have a direct correlation with severity.

In general, *inspiratory stridor* is associated with extra-thoracic obstruction of the airways (Brookes and Fairfax, 1982). The extra-thoracic region includes the part of the airway above the thoracic inlet.

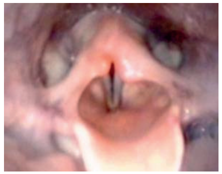
A polyphonic wheeze on the other hand normally reflects disease in small airways and is suggestive of asthma, especially if multiple wheezes are heard (Forgacs, 1973 and 1978). Obstruction in the intra-thoracic region of the airways usually produces *expiratory wheeze*, depending on the site and size of obstruction (Baughman and Loudon, 1989; Meslier et al., 1995).

Table II shows an overview of typical clinical features related to EILO at the supraglottic or glottic levels and EIA.

Table II

Comparison of clinical features of EILO and EIA

Description	EILO, Supraglottic level	EILO, Glottic level	EIA
Age	Adolescents	Adolescents and adults	Any age
Gender	♀ > ♂	♀ > ♂	♀ = ♂
Premorbid status	Athletes and active youngsters	Higher incidence of psychopathology	Not specific
Symptoms	Wheeze and dyspnoea Inspiratory distress Rapid onset during exercise and rapid resolution	Stridor and dyspea In- and/or ex-piratory distress. Rapid onset during exercise and gradual resolution	Wheezing and expiratory distress Rapid onset after exercise
	Throat tightness	Throat tightness	Chest tightness
Breath sounds	Low pitched mono-phonic inspiratory wheeze, low intensity extended inspirium	High pitched mono-phonic inspiratory wheeze, high intensity extended inspirium	High pitched mono-phonic expiratory low intensity extended experium
Predisposing factors	Extreme exertion odours, cold air	Exercise, panic, odours, infections	Exercise, infections cold air, allergies, stress

Physical examination	Inspiratory wheeze	Inspiratory stridor	Expiratory wheeze
Spirometry flow-volume loop	Plateauing of inspiratory portion	Plateauing of inspiratory portion	Blunting of the expiratory loop
Laryngoscopy	Collapse of supra-glottic structures	Paradoxical ad-duction of vocal folds	Normal, mild glottic adduction
			

Modified from: Bjornsdottir, *Exercise-induced laryngochalasia: an imitator of exercise-induced brochospasm* (Bjornsdottir 2000)

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One should also have in mind that a variety of conditions may affect the larynx and trachea and cause airway obstruction that can mimic symptoms caused by EILO. A careful examination of the patients should in most cases reveal the correct diagnosis in these cases. Table III summarizes possible entities of solid and dynamic upper airway obstructions that can cause stridor, and therefore also EIIS symptoms if patients are able to perform exercise (EILO is here excluded as dynamic obstruction).

Table III

Upper airway obstructions which may cause stridor

Description	Major Category	Examples
Solid obstruction:	Laryngeal stenosis (supraglottic, glottic, subglottic)	Subglottic stenosis, cysts, webs, cèles, haemangiomas, polyps
	Neoplasms (benign, malign)	Papilloma, carcinomas
	Infectious cause	Laryngotracheitis, epiglotitis, abscesses
	Allergic cause	Angioneurotic oedema
	Tracheomalacia, extrinsic (compression)	Neck masses, vascular rings
	Trauma	Fractures, oedema
Dynamic obstruction:	Tracheomalacia, intrinsic	Congenital
	Neurological disorders	Central nervous system lesions, recurrent laryngeal nerve lesions
	Vocal fold mobility disorder (VFMD)	Paradoxical vocal fold motion (PVFM), laryngospasm, laryngeal dyskinesia

1.7 Laryngeal function and aetiologocical aspects of EILO

The aetiology of EILO is complex and our understanding of the multiple factors inducing attacks is limited. One may argue that the aetiology of EILO will inevitably be related to some of the physiological aspects of the larynx and therefore these aspects are presented in more detail.

1.7.1 Laryngeal function

The valve mechanism

The larynx is described as an air passage, a sphincter device which folds and unfolds cyclically for ventilation and folds intermittently in increasing degrees for voice production, physical effort and deglutition (Fink, 1978). The two main tasks for the larynx are to secure the open airway and to protect the lower airway. The larynx accomplishes these conflicting tasks by its rigid cartilage skeleton, forceful ligaments and action of adductor and abductor muscles.

The larynx is protected from inspiratory collapse by its relatively rigid cartilage skeleton, particularly the cricoid cartilage, and muscular actions that provide support for the glottic- and supraglottic structures. The natural configuration of the larynx is such that the tapering subglottic cone resembles an inverted funnel and the expiratory flow rate is practically without hindrance. The free border of vocal folds and the shallow saucer-like contour of the floor of laryngeal ventricle capture the force of the inspiratory flow. Especially when supraglottic- or glottic structures are flaccid, this can be the cause of displacement in the air stream resulting in greater turbulence and diminished flow rate (Kashima, 1984).

The glottis is opened more widely during inspiration than during expiration in quiet breathing (Bartlett, 1989; Fink, 1975). The respiratory movements of the vocal folds are closely coordinated with those of the diaphragm and other muscles of the ventilator pump. The folds begin to separate slightly before the onset of diaphragmatic contraction.

During swallowing, the larynx is elevated to open the food passage and is tightly closed by the laryngeal sphincter mechanism. The most superior region, the aryepiglottic sphincter has a solely protective role. The vestibular folds behave as a one-way sphincter valve that traps air below the level of the larynx. Closure of the vestibular folds is followed by closure of the vocal fold sphincter (Fink, 1975).

In straining effort as in coughing, defecation and fixing the thorax, for improving the efficiency of the upper limbs, the larynx is hermetically closed (Fink, 1975; Naito and Niimi, 2000). Effort closure can consist of active adduction the vocal folds, active adduction of the vestibular folds and, active approximation of the thyroid cartilage to the hyoid bone (Fink, 1975).

Laryngeal respiratory function

The laryngeal valve mechanism can precisely regulate the trans-glottic pressure or resistance (Bartlett, 1989) and an important respiratory role of the larynx seems to be the regulation of resistance to airflow (Cole et al., 1993; Koufman and Block, 2008; Mathers-Schmidt and Brilla, 2005).

While hyperventilating and panting, the vocal folds are more widely abducted during inspiration than in the resting state, and the abduction is prolonged into or through the expiratory period, reducing expiratory laryngeal resistance (England and Bartlett, 1982).

During exercise, the ventilation rate may increase 20 to 30 times over resting values (Hurbis and Schild, 1991; Guyton, 1986). Elite athletes can achieve ventilation rates up to > 280 litres per minute (Carlsen and Kowalski, 2008). Transition from nasal to mouth breathing occurs when breathing reaches 25-30 litres per minute (Ferris et al., 1964). Active opening of the mouth lowers the larynx in the neck and thereby tends to widen the laryngeal orifice (Fink, 1975).

The mode of abduction of the arytenoids results in an efficient enlargement of the laryngeal bottleneck with a broadly pentagonal outline of the glottic area and permits intensive airflows (Fink, 1978). The increased glottic area significantly decreases the resistance to airflow in the larynx. The glottic area in expiration, in normal subjects, increases by 74% during exercise. This leads to a decrease of 67% in laryngeal resistance according to Baier (Baier et al., 1977; Hurbis and Schild, 1991).

Belmont and Grundfast, in their anatomical study, stated that the intrinsic muscles of the larynx serve not only to abduct and adduct the vocal folds but, clearly also assist in stabilisation of the arytenoids and presumably the attached aryepiglottic folds (Belmont and Grundfast, 1984). Together with the sub mucous collagenous fibres at the dorsal margin of the aryepiglottic folds (AEF), the poorly developed muscle fibres may render the folds sufficiently tense and resist inspiratory inward suction.

External and internal laryngeal muscles are involved in the adaption of the larynx lumen to increased airflow during exercise. The supraglottic part of the larynx is suspended in the hypopharynx by numerous muscles that exert dilatory forces on the laryngeal inlet; these muscles therefore serve as an integrated unit with the larynx in order to maintain patency of the airway. The following three muscles can provide support for the supraglottic part of the larynx and could clearly, with their vectors of force, interact to result in dilatation of the laryngeal inlet:

- The stylopharyngeus muscle; forms the lateral glossoepiglottic fold and the pharyngoepiglottic fold and inserts into the aryepiglottic fold.
- The palatopharyngeus muscle; inserts into the pharyngoepiglottic fold with the stylopharyngeus muscle along with portions of the stylopharyngeus muscle.
- The hyoglossus muscle; inserts into the hyoepiglottic ligament and appears to tilt the epiglottis forward (Belmont and Grundfast, 1984).

These muscles pull the epiglottis forward, the aryepiglottic folds are lengthened, and thinned and a possible instability of these structures should be prevented (Bent et al., 1996).

Contraction of the sternohyoid muscle is thought to drag apart the tissues internal to the thyroid cartilage lamina, notably the vocal-, vestibular-, and aryepiglottic folds (Fink, 1978). Accelerated laryngeal expansion produced by this mechanism would be negligible under eupneic conditions but is significant in a respiratory emergency. For example, in a competition between (elite) athletes, the last fraction of a millimetre of glottic enlargement, and thus the last fractional increase of respiratory flow, could be crucial. It has been speculated that the ossification of the lamina of the thyroid cartilage in the third decade of life involves a reduction in the flexibility of the athlete's larynx and consequently in its peak conductance (Fink, 1978).

1.7.2 Principles of aerodynamics

During exercise, the increased airflow has an influence on the laryngeal lumen that can be identified with principles of aerodynamics, i.e. Venturi and Bernoulli principles and Poiseuille's law.

Venturi principle

With the linear movement of a gas through a tube, lateral pressure decreases causing force acting towards a narrowing of the tube. The flexible airway is subjected to these forces; those parts that are loosely supported could fall into the airway during inspiration. Vigorous inspiratory efforts, particularly when associated with air hunger, create a relative increase in laryngeal pressure. The glottic and subglottic structures are fixed in size and that is why the tight supporting vocal ligaments are less affected by the Venturi principle. A model of this principle in the larynx is given in Figure 1.

Bernoulli principle

Bernoulli's principle is equivalent to the principle of conservation of energy. This states that in a steady flow, the sum of all forms of mechanical energy in a fluid or gas along a streamline is the same at all points on that streamline. This requires that the sum of kinetic energy and potential energy remains constant (Fajdiga, 2005). Manifestation at the glottis, of the Bernoulli principle, states that along a streamline the pressure is least where the velocity is greatest, provided that the total energy is constant (Figure 1)(Fink, 1978).

Poiseuille's law

Although this law counts for viscous fluids passing per unit time through rigid systems like capillary structures, it illustrates that resistance to flow in a given tube changes according to the fourth power of the radius of the lumen. The linear velocity of fluid increases when the volume flow rate is held constant and the calibre of the tube is reduced.

Laminar versus turbulent airflow

Laminar flow is silent, but above a critical velocity of flow, turbulence and vortices appear, and the oscillations set up by these irregular patterns of flow radiate sound. The intensity of the turbulence and the noise generated increase with the rising velocity of flow (Forgacs, 1978). The resistance to flow through casts and models of the human larynx is flow dependent, owing to this turbulence. The sharp reduction in airway cross-sectional area at the glottis gives rise to a central jet of high velocity in the upper trachea during inspiration which generates local turbulence.

1.7.3 Aetiological aspects of EILO

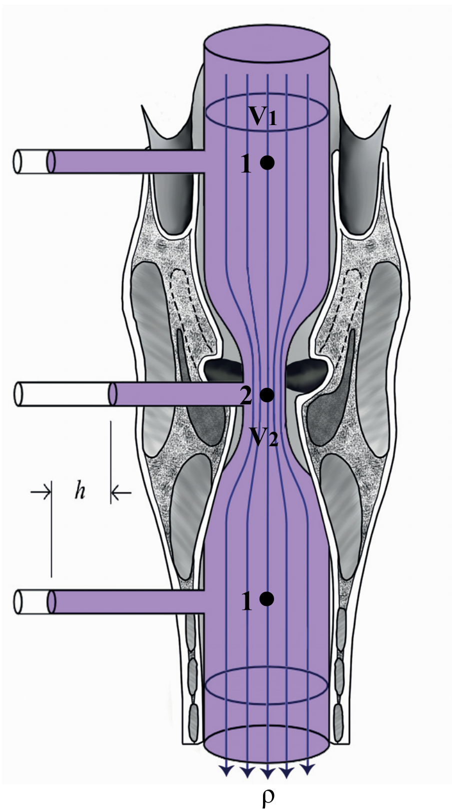
EILO at the supraglottic level

During the last three decades, several reports have been published on laryngeal collapse during exercise caused by prolapse of oedematous/swollen mucosa of the arytenoids, aryepiglottic folds, and/or epiglottic posterior displacement (Arora et al., 2005; Nonomura et al., 1996; Peron et al., 1988).

The movements of the AEFs are subjected to neural control (Logemann et al., 1992) however, factors responsible for this control mechanism are not yet understood in detail (Reidenbach, 1998). Central nervous system damage has been suggested as a common cause for mucosal tissue collapse of acquired redundant supraglottic prolapse into the laryngeal inlet (Nonomura et al., 1996).

Reidenbach suggests a possible reason for a non-physiological inward prolapse of the aryepiglottic folds towards the airway lumen, might be that the anchorage is insufficient and that the aryepiglottic folds may gain a pathologic ability of medial displacement during inspiration, which may be especially dangerous (Reidenbach, 1998). A sign of the forces at work is to be found in the position of the cuneiform cartilage relative to the vocal process (Fink, 1975): When the airflow through the larynx is relatively high, the cuneiform cartilages are normally further from the vocal processes.

The relationship between the velocity and pressure exerted by a moving fluid (liquid or gas) is described by a Venturi effect of the Bernoulli principle (Fajdiga, 2005) as described earlier. As the level of air flow increases, so do negative trans-mural pressure gradients that can result in collapse of the upper airways (Bjornsdottir et al., 2000; Mandell and Arjmand, 2003). This is illustrated in Figure 1.



Where h is the pressure difference between point 1 and 2, and ρ is the density of the fluid. V_1 *is the (slower) fluid velocity where the pipe is wider;* V_2 *is the (faster) fluid where the pipe is narrower.*

The figure is modified from an illustration about the Venturi effect at Wikipedia

Figure 1. Schematic picture, representing the Venturi effect and Bernoulli principle through the larynx

EILO at the glottic level

The closure of the glottic space is part of the protective laryngeal adductor reflex (LAR). An inappropriate or a paradoxical vocal fold motion (PVFM) may cause respiratory distress (Ayres and Gabbott, 2002; Shiba et al., 2007). PVFM is characterized by a paradoxical adduction of the vocal folds on inspiration (Wood and Milgrom, 1996), expiration (Echternach et al., 2009), or both (Goldman and Muers, 1991).

A hyper-functional reflex has been suggested as a potential cause for PVFM because this phenomenon can be initiated by different triggers like odours, perfumes and infections but also exercise-induced stress (Gimenez and Zafra, 2011; Taramarcaz et al., 2004; Kenn 2011; Ibrahim 2006).

Stimulation of the supraglottic mucosa induces a complex sequence of reflexive events resulting in adduction of the vocal folds and closure of the laryngeal inlet and, the swallow response. The involuntary efferent response travels by the vagus nerve. The same efferent vagal response influences the tonicity of laryngeal tissues (Andreatta et al., 2002; Ayres and Gabbott, 2002). Higher stimulus thresholds may be required to elicit the LAR response of glottic closure and swallowing. Prolonged or excessive stimulation can induce prolonged glottis closure or laryngospasm and apnoea. Alternatively, if the process of LAR is interrupted, inefficient coordination of airway protection may result. Afferent inputs might be related to supraglottic sensory impulses that show a loss of discrimination in the old age and in certain pathologic conditions (Reidenbach, 1998).

A causal link between PVFM and gastroesophageal reflux disease (GERD) has been suggested (Kenn, 2007; McFadden and Zawadski, 1996). Theories have been put forward that GERD may lower the threshold for stimuli to produce vocal fold spasm (Appelblatt and Baker, 1981) or, alter the LAR (Andreatta et al., 2002; Ayres and Gabbott, 2002). Belmont and Grundfast suspected a correlation between congenital laryngeal stridor and gastroesophageal reflux (GER) (Belmont and Grundfast, 1984). Lakin described an erythematous posterior surface of the arytenoids in a patient with

EILO, although the subject did not have any symptoms of gastroesophageal reflux (Lakin et al., 1984). Laryngopharyngeal reflux (LPR) is thought to cause several laryngeal symptoms like dysphonia, globus sensation, laryngospasm and PVFM (Belafsky et al., 2001; Koufman and Block, 2008). The respiratory obstruction caused by PVFM could be related to stimulation of vagal mediated reflexes by exposure of gastric fluids to supraglottic chemoreceptors (Loughlin and Koufman, 1996). It has been shown in animal models that the superior laryngeal nerves constitute the afferent limb of the PVFM reflex and that the recurrent laryngeal nerves constitute the efferent limb.

Theories have also been put forward indicating that psychological conditions or functional disorders as well as neurological diseases can cause PVCM. Maschka and co-workers proposed a classification scheme, later modified by Koufman and Block (Koufman and Block, 2008; Maschka et al., 1997). The scheme separates paradoxical vocal fold motion based on possible aetiology, both organic and nonorganic:

Organic aetiology: Brainstem compression, severe cortical dysfunction, laryngeal movement disorders, Parkinson symptoms, and drug-induced brainstem dysfunction, laryngopharyngeal reflux, asthma, or other causes for hyperactive mucosal tissue, drug-induced dystonic reactions (e.g. neuroleptic drugs).

Nonorganic aetiology: Factitious or malingering, conversion disorders, psychogenic stridor.

Vocal folds are unique as they are under both autonomic and voluntary control, and therefore a functional component of PVFM has been proposed by McFadden as well (McFadden, 1987). He postulated however, that factitiousness as cause for PVFM may be questionable because patients do not knowingly control the process and cannot volitionally reproduce the characteristic vocal fold motion. Though, it has been suggested that PVFM is associated with a number of psychological disorders, including anxiety and depression. It has been postulated that elite athletes may subconsciously convert performance anxiety into laryngeal closure, providing a physiological mechanism for some cases of ‘choking’ during sport (McFadden and Zawadski, 1996).

The majority of patients in published cases with PVFM are women between 20 and 40 years old. Among these patients, perfectionism, depression, and anxiety is common (Landwehr et al., 1996; Morris and Christopher 2010). On the other hand, PVFM has been demonstrated in new-borns as well (Omland and Brondbo, 2008). Typical presenting symptoms include stridor, dyspnea, inspiratory difficulty, throat tightness, voice change and in some cases, a feeling of choking and coughing (Wood and Milgrom, 1996).

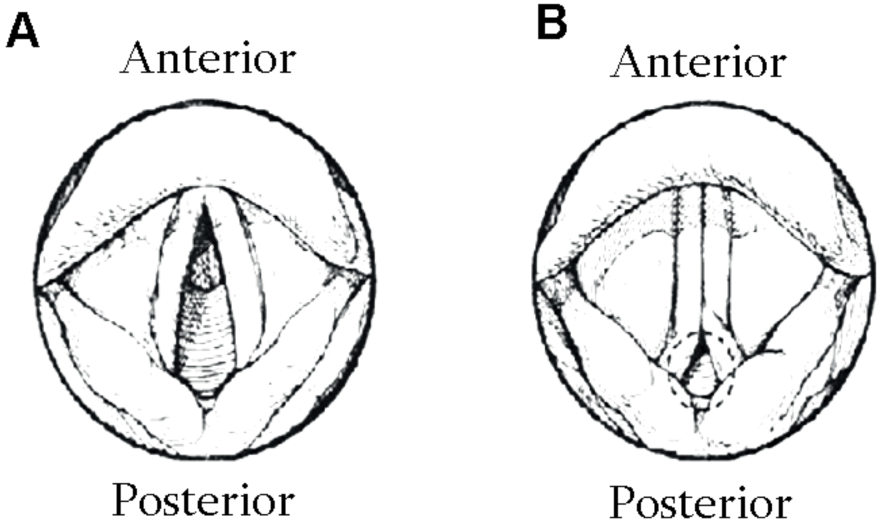


Figure 2A. Laryngeal finding in normal breathing and **2B.** laryngeal finding in PVFM

Illustration reproduced with permission from the author (Weiss, 2001)

1.8 Diagnostic procedures

The EILO diagnosis is based on patient history and examination preferably when the patients experience symptoms of respiratory distress.

Patients describe breathlessness and symptoms that often are mistaken as asthma-like. The distress may emerge during exercise or intense emotion during exercise and attacks do not respond to asthma medication. Most patients experience inspiratory wheeze or stridor. Symptoms like tightness of chest, pain in the throat or upper chest are reported. Some report a feeling of being choked eventually resulting in a panic attack. Attacks usually appear suddenly and disappear within a few minutes after the exercise has stopped.

The observer of an attack may hear a high pitched sound synchronous to each inhalation phase of the breath which indicates that the level of obstruction is located to the upper part of central airways, panic may occur during the end of an attack. The abrupt onset when triggered by exercise, relatively short duration and lack of symptoms at rest, points towards an obstruction at the laryngeal level.

Exercise-induced airflow constraint, in an otherwise normal larynx, becomes visible only at high airflow level, and because airflow rapidly decreases after exercise, pre- and post-exercise laryngeal examinations provide only limited information. A physical examination usually reveals normal findings by laryngoscopy between attacks but some authors have reported that subtle changes in laryngeal motion can be visualised by laryngoscopy also between attacks in these patients (Treole 1999). Spirometry investigations are described as useful tools; a flattening of the inspiratory section of the flow-volume loop is often cited as a typical finding (Vlahakis et al., 2002; Wood and Milgrom, 1996). However, flow-volume curves may often be inconclusive.

There are several previous reports on procedures of laryngoscopy during respiratory distress: England and Bartlett examined the laryngeal response to both exercise and hyperpnoea on an ergometer cycle among 5 healthy volunteers (England and Bartlett, 1982). Laryngoscopy during exercise on an ergometer cycle was further described by Hurbis and Schild who used a flexible laryngoscope to record laryngeal images while subjects breathed through a spirometer during endoscopy (Hurbis and Schild, 1991). The first study to continuously view the larynx throughout the entire exercise period, in combination with spirometry, was published by Bent and co-authors (Bent et al., 1996). A similar setup, with an incremental ergometer (stationary bicycle), was used by Beaty and co-workers in 1999 (Beaty and Hoffman, 1999; Beaty et al., 1999) and Fahey in 2005 (Fahey et al., 2005).

Flexible trans-nasal fiberoptic laryngoscopy in patients with ongoing symptoms therefore appears to represent a diagnostic gold standard (Beaty et al., 1999; Ibrahim, 2006). In most young people, a treadmill is a more relevant device than a bicycle when exhaustion is a major objective of the test (Garcia de la Rubia et al., 1998).

Although a continuous laryngoscopy during exercise may reveal the obstructions of the larynx as the cause for e.g. EIIS, the sensitivity and specificity of the tests should ideally be determined in order to fulfil important requirements for a clinical test.

1.9 Therapeutic challenges of EILO

Treatment of EILO has so far been based on relatively weak evidence. No randomized controlled trials utilizing objective outcome measures have been performed. Thus, firm evidence does not exist for any of the suggested treatment options and there is a need for future prospective randomized studies on this topic.

Management is based on exclusion of other causes for respiratory distress and discarding unnecessary medication. Acute attacks can be handled by on site manoeuvres e.g. panting or sniffing. A calm reassuring manner has been described in many case reports as an effective method of terminating acute attacks (Ibrahim 2006).

1.9.1 EILO at the supraglottic level

In patients with supraglottic type of EILO, and patients with hypertrophic supraglottic structures, treatment according to the principles outlined for pediatric laryngomalacia has been suggested and also proven successful, i.e. laser supraglottoplasty or epiglottopexy (Bent et al., 1996; Mandell and Arjmand, 2003; McClurg and Evans, 1994; Smith et al., 1995; Templer et al., 1981; Bent et al., 1996; Mandell and Arjmand, 2003; Smith et al., 1995).

Smith reported the removal of the corniculate cartilages by laser epiglottoplasty in patients with exercise-induced supraglottic collapse of tissue. Postoperatively, a visual improvement of the operated anatomical region was associated with marked improvement in aerobic endurance as measured by physical fitness testing (Smith et al., 1995). Subsequent to Smith's study, endoscopic supraglottoplasty was described by Bent and coworkers in 1996. It was performed with a carbon dioxide laser and suspension microlaryngoscopy; the corniculate region of the aryepiglottic fold was excised bilaterally. Repeat exercise testing after surgery showed complete resolution of the problem and could effectively reduce the redundant supraglottic tissue (Bent et al., 1996). Furthermore, others have shown that surgical treatment with supraglottoplasty or epiglottopexy can have a positive effect, with respect to symptom relief, in selected cases with the supraglottic type of EILO (Nonomura et al., 1996; Siou et al., 2002; Mandell and Arjmand, 2003; Whymark et al., 2006).

1.9.2 EILO at the glottic level

When it comes to treatment of EILO at the glottic level, more conservative treatment modalities are suggested. Patients are taught to focus attention away from the larynx and inspiration, to concentrate on active expiration using the anterior abdominal muscles, and to relax the oropharyngeal, intercostal, neck and shoulder girdle muscles (Andrianopoulos et al., 2000; Christopher et al., 1983; Goldman and Muers, 1991; Kayani and Shannon, 1998; Leo and Konakanchi, 1999; Maillard et al., 2000; McQuaid et al., 1997; Murry et al., 2004; Murry et al., 2006; Sullivan et al., 2001).

One should be aware that some of these techniques are used to treat attacks of respiratory distress that are not induced by exercise and therefore some of the suggested treatments are difficult to implement in a treatment for glottic EILO. This said, speech therapy, used to teach patients to relax the laryngeal muscles during inspiration, has been found to be very successful (Kayani and Shannon, 1998). Sullivan describes a treatment for PVFM in athletes; behavioural intervention to control symptoms of PVFM during exercise (Sullivan et al., 2001).

Nevertheless, it could be that certain techniques are not practical for those with exercise-induced PVFM, because the techniques would require stopping the athletic activity that was inducing the problem, which results in spontaneous resolution of symptoms anyway (Weinberger and Abu-Hasan, 2007).

Pharmacological treatment

In exercise-induced PVFM, Weinberger observed that an anticholinergic aerosol (Ipratproiumbromide), when used before exercise, can prevent paradoxical vocal fold adduction (Weinberger and Abu-Hasan, 2007). Pharmacological agents have otherwise been used to decrease the impact of PVFM triggers (Wilson and Wilson, 2006).

Inspiratory muscle training

Another treatment option could be inspiratory muscle training, to develop increased inspiratory muscle strength to reduce the perception of exertional dyspnea and to improve measures of maximal effort in athletes with exercise-induced paradoxical vocal fold motion (Mathers-Schmidt and Brilla, 2005).

1.10 Prognosis

Only sparse and even disparate results have been reported concerning prognosis of EILO and the long-term outcome is still unknown. Data from a retrospective study by Doshi and co-workers 2006 indicated that EILO at the glottic level (PVFM) is generally a self-limiting disorder (Doshi 2006). On the other hand Hayes and co-workers have, in a previous study, failed to show any improvement in threes cases followed for ten years (Hayes 1993).

2. The study

2.1 Aims of the study

The continuous laryngoscopy exercise test (CLE-test) had been developed at our hospital in order to visualize laryngeal motion during exercise in patients with exercise-induced respiratory distress (Heimdal et al. 2006). Clinical application of the CLE-test uncovered a need for a more objective evaluation of findings, and therefore a scoring scheme had to be developed.

Examination with CLE-tests revealed that some patients had severe obstruction at the supraglottic level of the larynx. Supraglottoplasty has previously been demonstrated as an efficient treatment for the supraglottic type of EILO (Bent et al., 1996; Mandell and Arjmand, 2003; Nonomura et al., 1996; Siou et al., 2002; Smith et al., 1995; Whymark et al., 2006). Patients with severe distress were often highly motivated for treatment in order to reduce their symptoms. Based on clinical selection, surgical treatment was therefore offered to patients who experienced serious respiratory distress related to severe supraglottic obstruction of the larynx. CLE-tests were used to assess the effect of surgery by comparing findings from pre-operative with post-operative CLE-tests.

The majority of our EILO patients were youngsters at the time of diagnosis (mean age 16.3 years). One could therefore hypothesise that development from a juvenile larynx to a more mature larynx i.e. increased inside diameter, stronger muscles and less flexible cartilage of the larynx, could reduce EILO. This question had to be addressed by re-examination of patients with a second CLE-test and a re-examination concerning symptoms during exercise, several years after EILO diagnosis.

Specific aims:

1. To apply the CLE-test on patients experiencing EIIS in order to assess the role of the larynx in this clinical scenario and to reveal type (level of obstruction) and severity of laryngeal obstruction if present.

2. To develop a CLE-score, that could be used to grade the severity of EILO as revealed by the CLE-test, and to test the validity and reliability of this new scoring scheme.

3. To investigate objectively the effect of surgery on severe supraglottic EILO by comparing pre-and post-operative CLE-tests in patients who had been surgically treated.

4. To study the natural course of the supraglottic type of EILO, and furthermore, to assess the long term effect of surgical treatment on the supraglottic type of EILO.

2.2 Methods

2.2.1 Study design

This thesis is based on an observational, combined cross-sectional and follow-up design. The study was approved by the Regional Ethics Committee and the Norwegian Social Science Data Services (Norsk Samfunnsvitenskapelig Datatjeneste, NSD). Informed written consent was obtained from all participating subjects.

2.2.2 Patients and volunteers

Patients (n = 166) were consecutively included, over a period of six years, from the paediatric outpatient pulmonology clinic and the department of otolaryngology, head and neck surgery at the Haukeland University Hospital, Bergen, Norway. Inclusion started in 2002 and concluded in 2008. Twenty volunteers (medical students and members of the ‘EIIS study group’) were recruited to demonstrate a normal laryngeal response-pattern to exercise.

2.2.3 Continuous laryngoscopy exercise test

The CLE-test provides visual and physiological information on laryngeal responses related to increasing ventilator requirements developed by incrementing exercise (Heimdal et al., 2006). A complete cardiopulmonary exercise test is combined with continuous laryngoscopy during exercise. Images from the upper part of the body of the patient and breath sounds are recorded simultaneously (Figure 3).

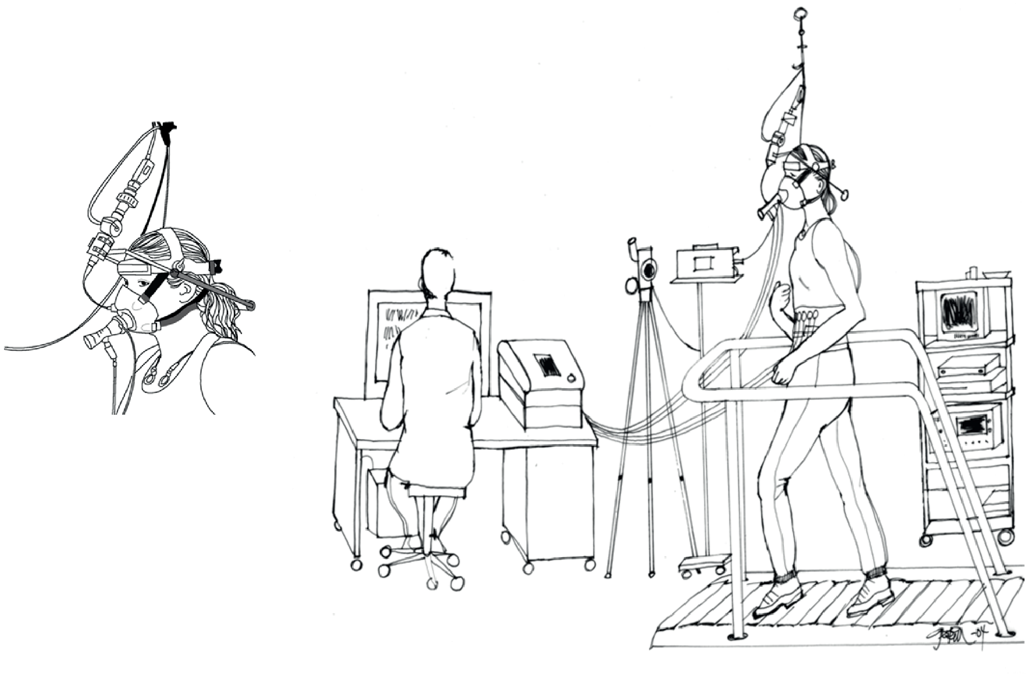


Figure 3. Continuous laryngoscopy exercise test

From: Heimdal; Continuous Laryngoscopy Exercise Test: A Method for Visualizing Laryngeal Dysfunction during Exercise (Heimdal et al., 2006)

Sound recordings

Sound recordings were made continuously throughout the examination to provide documentation that could be reassessed after each test. Laryngeal motion could be assessed simultaneously to respiratory noise which eased the differentiation between inspiratory and expiratory wheeze and stridor. The sound recordings could also be used together with the external video recordings to reveal additional information about the severity of distress.

Spirometry

The following variables of gas exchange were recorded: peak flow volume (FEV_1), forced vital capacity (FVC), minute ventilation (VE), maximal oxygen uptake (VO_2), respiratory quotient (RQ), maximal heart rate, respiratory rate and, tidal exercise flow-volume loops (extFVLs). Tidal exercise flow-volume loops were recorded several times during each test. The gas exchange parameters were recorded using the 'breath by breath' method (Cumming et al., 1978).

Evaluation

By reviewing the video recordings, movements, adduction at the glottic and the supraglottic levels could be assessed continuously as the subject exercised at different levels of effort. Respiratory noise and external recorded images were either evaluated simultaneously or at separate times to the laryngoscopy images dependent on specific aims of the different studies in this thesis.

2.2.4 Questionnaires

Questionnaires were used to reveal information about symptoms in relation to exercise, level of activity, influence of EIIS on daily life activities, use of anti-asthmatic medication etc. Also a visual analogue scale (VAS) was used by the patients to grade the severity of respiratory complaints during exercise (for more details see Appendix).

2.2.5 Surgical treatment

All surgically treated patients underwent supraglottoplasty, according to procedures used for patients with laryngomalacia and previous publications on EILO (Bent et al., 1996; Bjornsdottir et al., 2000; Lane et al., 1984; Olney et al., 1999; Siou et al., 2002; Smith et al., 1995; Zalzal et al., 1987). The site and amount of tissue removed was dependent on the severity of collapse at the CLE-test. A CO_2 laser was used to divide the aryepiglottic folds, to increase the anterior-posterior distance of the supraglottic structures. Hereafter, the redundant mucosal tissue, overlying the cuneiform tubercles and the upper part of the cuneiform tubercle, was removed, either by CO_2 laser or cold instruments, or a combination of these.

2.2.6 Statistical analyses

In study II, kappa analysis according to Altman (1991) was performed in order to reveal inter- and intra- observer agreement. Correlation analyses were performed with Spearman ρ when laryngeal observations were compared with clinical observations of symptoms. Concordance between scores was assessed with Chronbachs's α and Chi-square test were used to assess differences between patients and controls.

In paper III ANOVA analyses were performed in order to compare groups and the first versus second CLE-tests were compared with Student *t*-tests. The Wilcoxon Sign Rank as well as Mann Withney test was used to validate the *t*-test.

2.3 Summary of results

2.3.1 Paper I

Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways

We aimed to study laryngeal function in exercising humans experiencing symptoms of EIIS by using the CLE-test. We also wanted to study laryngeal function in symptom negative controls. We observed that patients compared to controls showed a more pronounced adduction of the supraglottic structures concomitant with symptoms of respiratory distress (EIIS). A primary adduction of the glottis was seldom observed as cause for EIIS. The presence of structural obstructions was observed in approximately 10 % of patients and could cause symptoms similar to EILO. We concluded that the CLE-test could safely be applied to study the larynx during an exercise treadmill test.

The normal laryngeal response and moderate to severe adduction of laryngeal structures during exercise, is illustrated by Video 1 and 2 respectively, which can be found in the online version of this publication at:

http://dx.doi.org/doi:10.1016/j.rmed.2009.05.024

2.3.2 Paper II

Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations

This study was performed in order to develop a grading scheme that included the level and severity of laryngeal obstruction during exercise. The reliability and validity of this scoring system was assessed.
A grading scheme (CLE-score) was developed, including scores related to obstruction at the supraglottic- and glottic level of the larynx during exercise, as demonstrated on videos from the CLE-tests (Appendix). Inter- and intra-observer

reliability was calculated with kappa-scores for each level (glottic, supraglottic), and moment of scoring (moderate and maximal intensity). Overall outcome showed moderate to very good inter- and intra-observer agreement. We therefore concluded that the CLE-score was reliable and also valid as there was a significant correlation between the CLE-scores and the severity of respiratory distress symptoms as assessed both by patients and by observers.

2.3.3 Paper III

Surgical treatment of exercise-induced laryngeal dysfunction

Laser assisted supraglottoplasty is a well-known procedure for laryngomalacia in new-born and young children. The method has been described and recommended as a treatment for adult type of laryngomalacia caused by e.g. redundant mucosa overlying supraglottic tissue. Some of the patients examined in this project were severely disabled by their EILO. Therefore we decided to use the supraglottoplasty to treat patients selected by strict clinical criteria i.e. major influence of symptoms on their quality of life and physical capacity, severe supraglottic laryngeal obstruction as observed during CLE-tests, and patients highly motivated for treatment in order to reduce symptoms.

The aim of this study was to use the CLE-test to assess the effect of supraglottoplasty, on exercise-induced laryngeal obstruction, by comparing pre-and postoperative CLE-test findings. Nine out of 10 patients were satisfied with the results of treatment. They subjectively felt able to breathe more easily during exercise. The CLE-test showed an improvement in the ability to keep the supraglottic structures in abducted position both at moderate and maximal exercise. Inspiratory collapse of these structures was not shown in any of the treated patients. Spirometric parameters did not change significantly but, there was a significant improvement of symptoms on the VAS scale on symptom severity ($P = 0.002$, statistics not described in original publication). To date, none of the patients have experienced complications related to this surgical procedure.

2.3.4 Paper IV

Exercise-induced laryngeal obstruction; natural history and effect of surgical treatment

In this retrospective observational study, we aimed to assess the natural course of supraglottic EILO and at the same time, study long-term effects in patients who had been treated surgically for supraglottic EILO. Changes in symptoms of exercise-induced breathing distress, level of activity and the impact of symptoms on daily life activity, were addressed in questionnaires sent by mail. Most patients experienced a symptom relief but, more so in surgically treated patients than untreated patients. Comparison of pre- and post-operative CLE-tests showed a significant improvement, in the ability to keep the larynx open while exercising, in the surgically treated. On the other hand, only minor changes were observed in laryngeal motion in 14 untreated patients re-tested with the CLE-test. We concluded that EIIS due to supraglottic EILO does *not* seem to recover spontaneously in young patients and patients with severe supraglottic EILO may benefit from surgical treatment, even after 2-5 years of follow-up time.

2.4 Discussion

In this thesis the CLE-test has been applied to a large series of patients experiencing EIIS. A specific CLE-score system has been developed and reliability, as well as validity, of this CLE-score has been tested. Clinically selected patients with disabling or severe supraglottic type of EILO were offered surgical treatment. Surgically treated patients have been examined pre- and post-operatively with the CLE-test. EIIS patients were re-evaluated as to EIIS symptoms with a questionnaire and a selected group of patients with supraglottic type of EILO, who were not surgically treated, were also invited to perform a second CLE-test. This discussion focuses on the methods used and the results obtained, with special attention given to the implication that these results have on the present understanding of EILO as a phenomenon, how it should be assessed and treated.

2.4.1 Methodological aspects

Inclusions

The included subjects were either admitted to the departments of paediatrics or otolaryngology/head and neck surgery due to unresolved exercise-related dyspnea, and/or obstructing sensation at the laryngeal level during exercise. Most subjects had been subjected to a screening maximum exercise treadmill test according to a standard EIA protocol. Patients with observed inspiratory distress or stridor, or a clearly abnormal breathing pattern during on-going exercise, were invited to participate in the study. Some patients were included due to persistence of abnormal flow-volume loops despite adequate asthma therapy.

Controls

The 20 volunteers were in general older than the patients (mean 22.7 to 16.3 years, respectively). It is possible that the larynx response to exercise changes from childhood to adolescence and therefore controls should ideally be at similar age as patients. However, for ethical reasons, we found it somewhat difficult to use agedmatched controls as the CLE-test represents a certain degree of discomfort, particularly in children.

Surgically versus conservatively treated patients

In the fourth paper, symptoms at the follow-up of the surgically treated (ST) patients were compared to symptoms of the conservatively treated (CT) patients. These two groups could not be perfectly matched as the patients were selected for surgery based on clinical and not on random selection. Ideally the ST and CT patients would have been compared in a prospective randomized study however, this was not done but, most patients that were treated surgically were included in the middle part of the study. Thus, patients included in the first part of the study and therefore not offered surgery, could be viewed as "historical" controls. An attempt to find matched pairs in these two groups revealed that they indeed were, to a reasonable extent, comparable as to age, gender and level of CLE-scores at the time of diagnosis.

Expectation concerning treatment effects, as well as perception of symptoms, may have been influenced by the different admittance to treatment in the study presented in paper IV. One may argue that patients who were treated surgically would reckon this to be a privilege and therefore overestimate the effect of surgery based on the eager to please effect. On the other hand we experienced that a few surgically treated patients may have had unrealistic expectations to the effect of surgery and therefore to some degree expressed disappointment to the effect of surgery although the post-operative CLE-test results showed improved capacity and reduced obstruction of the larynx. Therefore this effect of expectation could result in a negative response as well. The comparison of the CLE-test ensured a more objective comparison than just symptom scores would have offered and thus is an advantage of this test.

2.4.2 The CLE-test

Normal versus pathological laryngeal motion

Visualisation of the larynx during progressively strenuous exercise demonstrates dilatation and antero-rotation of the supraglottic part of the larynx, thinning and elongation of the aryepiglottic folds, epiglottic flattening against the base of tongue, and progressive glottic abduction (Beaty and Hoffman, 1999; Beaty et al., 1999; Bent et al., 1996).

Bent and co-workers have previously reported that a slight adduction in the ary-epiglottic folds can also be demonstrated in control subjects during heavy exercise (Bent et al., 1996). We observed similar findings in our control subjects indicating that these findings might be considered normal. Therefore we took these observations into consideration when deciding which observations should be focused on in the CLE-score scheme and how the grading steps should be made in order to differentiate between normal and pathological laryngeal motion.

Differentiation and grading of laryngeal obstruction

The grading scheme developed can be used to assess obstruction both at the glottic and the supraglottic level. The scheme was found to be reliable and valid according to the requirements for these qualities. However, there are some characteristics of laryngeal obstruction that are not possible to assess by the scheme. One example is the retroflection of the epiglottis which is a less common type of laryngomalacia and also observed during exercise in adolescence in our study. It can be discussed whether the scheme should be modified in order to include this less common type of obstruction in the total score.

The grading scheme differentiates between obstructions occurring at moderate and maximal effort. Moderate effort is determined as the level of exercise when the mill runs so fast that the subject has to change from walking to running. We decided to assess obstructions twice during the test in order to increase the potential number of scores. Another advantage with this double assessment is the possibility to detect early signs of abduction at each of the two levels and distinguish which obstruction comes first.

CLE-score validation

There are only a few studies where normal laryngeal motion during exercise is differentiated from pathological obstruction e.g. Bent and co-workers (1996). In order to separate normal findings from pathology, one should ideally be able to find a threshold value of obstruction that separates these from each other. In order to decide upon a more precise cut-off point for the CLE-score, that separate normal laryngeal function from pathological obstruction, more volunteers should have been examined. This said, we still consider the suggested cut-off level of sum score in paper III to be a good estimate because the validity of the CLE-sum score is based on observations and symptom scores from sixty patients and volunteers (Figure 3 in paper II and EILO grading system in the Appendix). More population based studies are needed, including symptomatic and non-symptomatic subjects, in order to define more precisely, the grade of obstruction that separates normal from pathological laryngeal responses to exercise. Although the CLE-score is found to be reliable and valid, the CLE-score should also be compared to alternative methods and used in population studies in order to define its sensitivity and specificity.

2.4.3 Stridor and wheeze

Goldman differentiated wheeze from stridor by the pitch of the tone (Goldman, 1997). Both stridor and wheeze were sometimes audible during the CLE-test of a subject. We found that 135 out of 151 patients (89%) developed wheeze and 67 (44%) produced inspiratory stridor, often combined with wheeze. When comparing sound recordings with video recordings of the larynx during CLE-tests, we found that high pitched stridor correlated with exercise-induced obstruction at the glottic level. However, the symptom of audible respiratory distress should be used with care when diagnosing patients without laryngoscopy (Zwartenkot et al. 2010).

2.4.4 Effects of surgery on supraglottic EILO

We observed that surgical treatment at the supgraglottic levels seemed to have a positive effect, not only on the supraglottic obstruction but, also on the concomitant obstruction at the glottic level, i.e. a reduced obstruction as measured by the supraglottic "D" score correlated with a reduced glottic "C" score. We can only speculate on mechanisms for this interesting observation as we have not yet been able to examine this phenomenon further. Apparently, surgery increases the diameter of the laryngeal entrance, which may reduce flow resistance by preventing supraglottic tissue collapse (Bjornsdottir et al., 2000; Damrose, 2008; Kashima, 1984; Mandell and Arjmand, 2003). A decrease in air-flow resistance could possibly decrease adductional forces to the vocal folds, as explained by Bernoulli's law, to give the muscles which abduct the vocal folds, a better way to perform adequately (Fajdiga, 2005; Kashima, 1984).

Supraglottic stenosis and interarytenoid adhesion, secondary to the supraglottoplasty, have been described as a result of the procedure among children treated for laryngomalacia (Denoyelle et al., 2003). The complications are rare and mainly seen in cases with additional congenital anomalies. Nevertheless, it should be taken into consideration also for the supraglottoplasty in supraglottic EILO.

Mandell and Arjmand suggested that endoscopic supraglottoplasty should be performed in two phases to prevent supraglottic stenosis (Mandell and Arjmand, 2003). Although repeated procedures would allow CLE-test evaluation between them, we recommend that the procedure of choice in each case is determined based on the evaluation of pre-operative CLE-test.

2.4.5 Prognosis of EILO

It has been postulated that laryngeal growth at puberty would be sufficient to overcome the tendency toward inspiratory laryngeal collapse (Zalzal et al., 1987). As the child grows, the tissues become firm and are resistant to inspiratory forces and thus should outgrow the condition. In paper IV we observed that only 3 out of 14 re-tested subjects showed laryngeal motion that we consider normalized according to the CLE-score. Although the number of examined patients is too small in order to draw any firm conclusion we cannot state that supraglottic type of EILO is cured when patients reach adulthood. On the other hand patients reported fewer EILO related symptoms as well as reduced level of activity which indicates that EILO as a problem is reduced in older subjects because they are less active than before. The relationship between age and EILO seems to be more complex than only a matter of laryngeal maturation and should be further addressed in forthcoming studies.

2.4.6 Age and gender in relation to EILO

Age

Most patients were teenagers. The aryepiglottic folds and the arytenoids, which are relatively larger at this age than in adults, create a smaller supraglottic lumen. The epiglottis is relative long and can be curled on itself (Hast, 1970). The elongated, tubular epiglottis and closely approximated aryepiglottic folds could be drawn inward with inspiration because of more pliable and unsporting framework. The continuous movement, vibration and irritation of these tissues could cause inflammation and oedema, which further worsens the stridor. This is possible because the arytenoid tissue is less firmly attached than normal.

Gender

Previous reports have concluded that EILO is more often revealed in young females than males (Bittleman et al., 1994; Bjornsdottir et al., 2000; Fahey et al., 2005; Lakin et al., 1984; Smith et al., 1995; Stone, 1995). We also found an increased female to male ratio as 71% of patients in our study population with positive EILO were girls with little difference in the mean age between girls and boys i.e. 16.2 and 16.4 respectively. It is pertinent to ask why females seem to be more often affected by EILO than males at the same age. One potential explanation is the fact that the larynx in females is different to the larynx in males, e.g. smaller inner diameter. According to observations from anatomical studies, the laryngeal inlet does not show significant gender differences when evaluated in (pre) puberty, however a considerable divergence in larynx dimensions occur during the development period (Castelli et al., 1973; Kahane, 1982; Wysocki et al., 2008). At a given airflow the female larynx may therefore be more prone to collapse due to the Bernoulli forces (Bent et al., 1996). On the other hand females do not develop flow rates as high as males.

Another explanation could be that the female larynx tends to grow earlier than the larynx in males. During growth the supraglottic structures do not have much support from cartilages and connective tissue (Fried Marvin P, 2009). Another factor might be estrogens which are reported to have a hypertrophic effect on laryngeal mucosa, as well as to cause an increase in secretion from the laryngeal glandular cells and so decrease the laryngeal lumen (Fried Marvin P, 2009). In addition, the differences in relative diameters of the upper part of the airways may play a role in this matter. The length of the pharyngeal cavity and the nasal opening has a significantly faster rate of growth in boys than in girls, especially during pubertal years.

Although EILO is more common in females, the condition does not seem to be more severe in females than males as there was no correlation between severity of laryngeal obstruction and gender in our study population. However, the relation between severity of EILO and gender needs to be addressed further in future population studies.

2.4.7 Aetiological aspects of EILO

One might hypothesise that there is a threshold in airflow which triggers the supraglottic structures to collapse and, if airflow velocity could increase infinitely, everyone would develop enough negative pressure in the laryngeal inlet for the supraglottic structures to collapse. The threshold seems to depend on the stability of the lateral structures to keep the aryepiglottic folds abducted. Fahey described the phenomenon of EILO only at near peak exercise and not as a progressive finding during exercise (Fahey et al., 2005). The onset is abrupt and heralded by oscillation, or vibration of the arytenoids area, as if in response to high airflow.

A correlation between EILO and paediatric laryngomalacia seems not to be likely: None of our patients had a history of breathing problems in early childhood and in the literature, there is only one description of a patient with exercise-induced laryngeal obstruction who also had a history of laryngomalacia (Mandell and Arjmand, 2003).

In our studies on EILO, redundant tissue removed from the cuneiform area was histologically investigated in a few cases. Besides normal squamous epithelia from the larynx, squamous epithelia with chronic inflammation and myxoid, degenerative connecting tissue, were observed. If there is a correlation between chronic inflammatory disease like laryngopharyngeal reflux (LPR) and EILO, it is still too early to decide.

Supraglottic EILO causes a narrowing of the inlet of the larynx. By Bernoulli's law, trans-luminal pressures will be greatest in this narrow, noncompliant space. During extreme exertion the relative contribution of the upper airway to total pulmonary resistance increases and as higher negative trans-laryngeal gradients develop, inspiratory collapse of a poorly supported supraglottis can occur (Ferris et al., 1964). Although an increasingly negative inspiratory force predisposes to EILO, other factors must be involved in the subset of patients who experience this problem (Bent et al., 1996).

In our study, a paradoxical adduction of the vocal folds developed most often after obstruction at the supraglottic level (88 out of 113 patients) and panic reactions were observed only in a minor number of patients. Similar observations are also described by Tilles and co-workers (Tilles and Inglis, 2009).

One potential explanation for the glottic closure can be weakness of the muscles which are stabilizing the arytenoids and keeping them in upright positions. If the arytenoids are not kept upright, the vocal processes will rock downward and inward. This will reduce the glottic chink to less than the critical diameter and set up the condition for aerodynamic inspiratory obstruction (Fink, 1975). An explanation for (exercise-induced) PVFM could therefore be that the Bernoulli effect, due to respiratory airflow through the throttle, will cause closure of the glottis whenever the folds are separated by less than 3 millimetres (Fink, 1975). There could also be a fatigue phenomenon in structures which causes an inability to abduct the vocal cords properly.

We observed that only 4 out of 113 patients had laryngeal obstruction at the glottic level only, i.e. no concomitant obstruction at the supraglottic level. One might speculate that these few patients are suffering from a different pathological mechanisms inducing EILO than the majority of patients. Further studies have to be completed to give an answer to whether or not there is an association between EILO (either glottic or supraglottic) and psychological influences.

Hyper sensitivity and protective reaction

Reflexes play an important role in laryngeal function; respiration, swallowing and airway protection from aspiration. Peripheral afferent nerves in the larynx provide a variety of physiological inputs through specialized end organs, including pneumoreceptors, chemoreceptors, thermo receptors, proprioceptive and mechanoreceptive afferent nerves Mechanical or chemical stimulation of the supraglottic mucosa or direct stimulation of the superior laryngeal nerve activates the laryngeal adductor reflex to protect the airway from aspiration and asphyxiation of secretions and food (Thompson, 2007). One of the patients, treated with supraglottoplasty, developed breathing difficulties in cold weather and was treated with $ß_2$ agonists in severe circumstances. It is possible that surgery changed the threshold of response in the protection mechanism of the supraglottic structures in this patient (Sant'Ambrogio et al., 1995).

In the study cohort, 24 % of the patients reported that they had (airborne) allergies. This percentage is similar to that in a normal population. As we have not studied this feature yet, we cannot give any information concerning the correlation between allergy and EILO. EILO and airway hyper responsiveness seem to occur with the same frequency in the general population and together they account for 96.5% of the cases of exercise-related symptoms (Christensen et al., 2011).

It has been reported that topical anaesthesia and minor manipulations do not affect the resistive behaviour of the larynx (Baier et al., 1977; Cole et al., 1993). We obtained similar results when comparing patients treated with and without topical anaesthesia in the nose (personal communication/not published).

Laryngopharyngeal reflux

Cukier-Blaj and co-workers, observed that patients with PVFM exhibited a high prevalence of symptoms related to LPR and markedly reduced laryngeal sensitivity; consistent with a sensory deficit hypothesis for these patients (Cukier-Blaj et al., 2008). Various extrinsic stimuli could trigger reflexive closure of the vocal folds at pathologically low thresholds. It is not known if there is a correlation between LPR and EILO. In our studies, only one patient, with GER symptoms, was known. However, only 60% of patients with proven GER, seem to develop symptoms like heartburn (Smit et al., 2000).

Belafsky developed an eight-item clinical severity scale (reflux finding score, RFS) based on findings obtained during fiberoptic laryngoscopy, including subglottic oedema, pseudo ulcus, ventricular obliteration, erythema/hyperaemia, ulceration/granulomas, oedema and pachydermia. The RFS could document treatment efficacy in patients with LPR (Belafsky et al., 2001). We have not measured pH values in the oesophagus in our study so far but have re-examined the video-recordings, from all patients included, based on the methods described by Belafsky. Interestingly we were able to find different RFS values between patients and volunteers and a correlation between RFS and sum score at CLE-test was observed (not published data). These findings should be interpreted with caution as there is a lack of specific diagnostic tests to confirm LPR. According to the conclusions of Mahieu, laryngeal symptoms in LPR are non-specific and are difficult to distinguish from other causes of upper respiratory tract inflammation (Mahieu, 2007). It might be that our unpublished findings point towards the presence of a generalised oedema, rather than LPR in our patients. The hypothesis has to be verified by pH measurement in future studies of EILO patients.

A possible causative correlation between LM and LPR is illustrated in Figure 4.

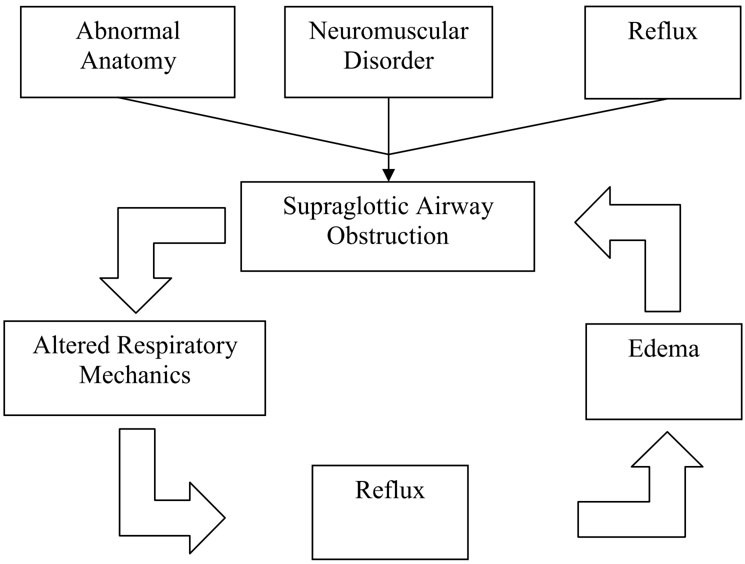


Figure 4. Possible relationship between LM and LPR

From Matthews; Reflux in infants with laryngomalacia (Matthews et al., 1999)

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Neuromuscular dysfunction

Possible causes for PVFM can be central nervous lesions like brainstem compression, cortical dysfunction, or an associated finding in patients with movement disorders, causing breathing difficulties through obstruction in the larynx (Koufman and Block, 2008; Maschka et al., 1997; Shiba et al., 2007). Hypotonia of the stylopharyngeus-, palatopharyngeus- and, digastric- muscles, secondary to neuromuscular dysfunction, has also been proposed as a cause for congenital laryngomalacia (Belmont and Grundfast, 1984).

In our studies, there was one patient with a known unilateral vocal fold paralysis due to central nervous damage. Another patient with redundant, unilateral mucosal tissue from the arytenoids did not show pathology besides this finding.

Temperature and humidity

The severity of EIA symptoms is dependent on and modified by, the temperature and humidity of inhaled air (McFadden and Gilbert, 1994). Several patients in our study participated in winter sports (biathlon, cross country skiing) and reported more symptoms in cold, dry air. Patients who trained in a warm and humid environment like swimmers, experienced the same symptoms. Langdeau described a higher prevalence of respiratory distress symptoms in athletes training in cold or humid air, though there was a correlation between these symptoms and airway hyper responsiveness, explored by a methacholine test (Langdeau et al., 2000).

It is possible that certain conditions related to air e.g. low temperature, increased humidity and the presence of irritants, can trigger EILO by introducing hypersensitivity of laryngeal mucosa. This has to be investigated in future studies.

Athletic fitness

Bent and co-workers (1996), hypothesized that highly conditioned athletes, who can generate higher airflow velocity for longer durations, may be at greater risk for EILO (Bent et al., 1996). Beaty suggested that high inspiratory airflow seems to be required for EILO and therefore it is most likely to occur in physically active individuals (Beaty et al., 1999). We got the same impression; a substantial proportion of the studied subjects developed a moderate to severe supraglottic collapse whilst only reaching 80% of their maximal calculated heart rate. In our studies, 20 athletes were competing at (inter) national level. One might speculate that these would probably not develop any collapse of laryngeal structures if they had not been as active as they were.

Psychological aspects

In a review article on psychogenic respiratory distress, 171 cases of PVFM were collected from literature. Psychiatric diagnoses were varied and only in 7% was no formal psychiatric diagnosis made (Leo and Konakanchi, 1999). Husein stated that PVFM is associated with conversion disorder, representing a physical manifestation of underlying psychological difficulty (Husein et al., 2008).

Little is known about a possible psychogenic influence on EILO. Patients experience more symptoms in stressful situations like competitions compared to training situations (Ommundsen et al., 2006) and a possible reason may be that in such a situation, the subject is more influenced by competition anxiety and develops a paradoxical vocal fold motion. One of our patients admitted, in the follow-up examination, that she was under parental stress during competitions at the time of diagnosis. She actually acknowledged that symptoms like stridor and panic reactions, gave her secondary gain and a reasonable way out of a stressful situation. Although this single patient story cannot be generalised, it illustrates that EILO is not a straight forward diagnosis. Social as well as psychological influences have to be taken into account and collaboration with a psychologist could be helpful when patients with EIIS symptoms are taken care off (McQuaid et al., 1997).

2.4.8 Management

Treatment of EILO has been based on relatively weak evidence. Awaiting future prospective randomized studies, we have based our strategy on the available literature, our own clinical experience and following the algorithm presented (Flow chart). Triggers and contributing factors should be identified, removed or treated, if possible.

Management of EILO must include the exclusion of extra-laryngeal pathology causing respiratory distress during exercise, as approximately 10% of patients had structural pathology in the proximal airways.

One must also be aware that excessive focus on high performance in athletes may trigger or aggravate symptoms of EILO. Therefore supportive counselling is important.

Patient information

The laryngeal video recordings should be presented and explained to the patients and their parents. Information on normal laryngeal function and possible causes for laryngeal obstruction should be focused on. One should instruct patients on how to cope with their problems and to focus on the expiration and not on the inspiration. We told the patients to reduce the intensity slightly and to inhale through the nose (sniff) if they experienced respiratory distress. This information alone seems to reduce anxiety and ease the problems for many patients and further treatment is therefore often not necessary.

Selection of treatment

The optimal treatment protocol for the different types of EILO is still to be determined. We offered surgery to 24 patients with supraglottic type of EILO based on clinical selection, as previously stated.

Surgical treatment must be performed with great care. The severity of symptoms, findings from CLE-test video recordings and patient motivation for treatment should be reviewed thoroughly. Potential gain should be weighted towards possible complications of the surgical procedure. Especially the last aspect, concerning complications, should be discussed carefully with the patient and/or care takers before the procedure is performed.

3. Conclusions

Based on the results of the studies in this thesis it can be concluded that:

The CLE-test is relatively easy to use on a routine basis for evaluation of patients with EIIS, and laryngeal obstruction can be visualized, if present, by the CLE-test in these patients.

The obstruction of the larynx in EILO patients is most often due to an inward rotation of the aryepglottic folds followed by a narrowing of the glottis. Only in rare cases is the EILO condition caused by a glottic adduction only.

The CLE-score is a reliable and valid method for assessing the grade of laryngeal obstruction.

Surgery with supraglottoplasty can be an adequate treatment with long lasting effects in strictly selected cases i.e. supraglottic EILO with severe obstruction and symptoms, in patients highly motivated for treatment.

Symptoms of EILO in adolescents generally decrease after 4-5 years, but findings of persistent laryngeal obstruction, when patients are re-tested, indicate that the EILO as a condition is not spontaneously cured.

We recommend that patients are advised to focus on breathing techniques in order to cope with their distress. Further studies are needed in order to establish a consensus concerning treatment protocols that have been suggested by others.

Based on clinical experience from our studies and reports from others, a flow chart for diagnostic and management of EILO is proposed. The different options need to be studied and confirmed in future randomized controlled studies (Figure 5).

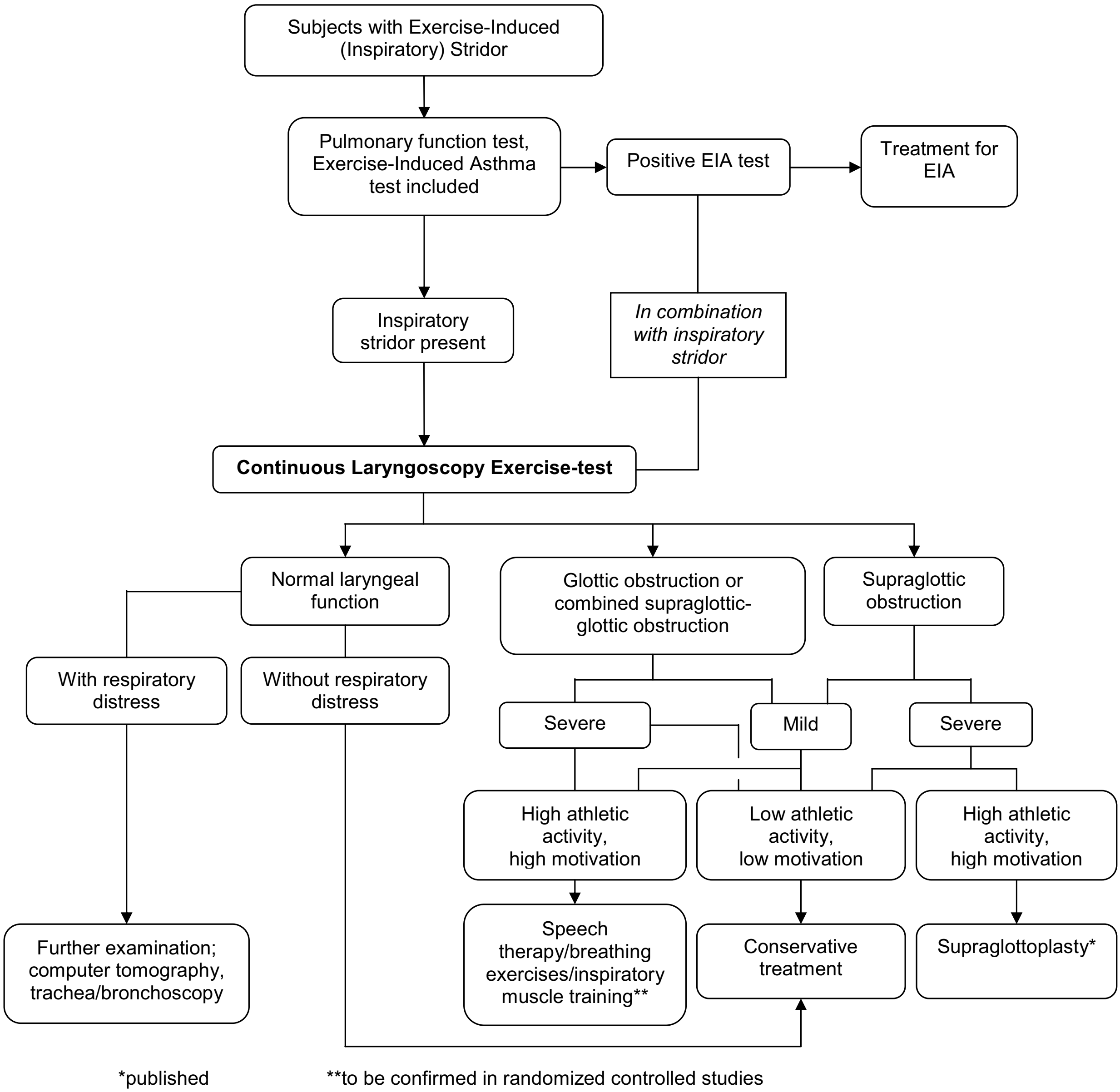

Figure 5. Proposed flow chart for diagnostic procedures and therapy of EILO, based on clinical experience until now. Prospective studies are required to establish evidence-based treatment algorithms for patients with EILO

4. Future perspectives

There is a need for population based studies to reveal the prevalence of EILO.

Randomised, controlled treatment studies, including speech therapy, breathing exercise treatment, inspiratory muscle training, versus surgical treatment should also focus on psychological influences behind this phenomenon.

A better knowledge of normal and age-related changes in laryngeal motion during exercise is required. There is a need for examinations of flow resistance in the larynx during exercise, in order to get a more thorough understanding of pathophysiological mechanisms causing the EILO phenomenon.

Gastroesophageal reflux disease in EILO patients has to be studied in the future to find out if there is a connection between the two features.

There is a need for an agreement on nomenclature and classification, as well as standardized diagnostic procedures, of EILO if international multicentre studies on randomized controlled therapy are to be carried out.

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Curriculum Vitae

The author of this thesis was born on June 2nd 1969 in Arnhem, the Netherlands. After finishing secondary school at the van Lingen College in Arnhem, he enrolled for his medical studies at the Utrecht University in 1989. In 1997 he obtained his medical degree before he started working as a resident at the surgical department at the St. Jansdal Hospital in Harderwijk.

In February 2000, he emigrated to Norway and started working as a general practitioner in Fåvang, community of Ringebu. In November 2001, he started his training in Otorhinolaryngology, at the department of Otolaryngology, Head and Neck surgery, Haukeland University Hospital in Bergen, Norway under the supervision of Professor Jan Olofsson, head of the division Head and Neck, and became certified in 2006.

During his residency at the Haukeland University Hospital, he took part in the exercise-induced inspiratory stridor studies from 2004 and made the basis for this thesis. From 2006, he trained in laryngeal pathology and management under the supervision of associated Professor John-Helge Heimdal until 2008. Hereafter, he moved back to the Netherlands where he started as a consultant at the department of Otorhinolaryngology at the Röpcke-Zweers Hospital in Hardenberg and he remains in that position to date.

He is married to Tanja Slegers and they have a daughter Marthe (2010).

Appendix

Questionnaire **ID:** **Date:**

Here are two pages with questions that deal with exertion as triggering factor for breathing difficulties.

We ask that you please answer all the questions before the line no matter what your current degree of symptoms. If you still have some degree of breathing difficulties, we ask that you please also answer the questions below the line on page 2.

Please check the box:

Are you still active?
- ☐ **I am as active now as I was at the time of the examination (on treadmill)**
- ☐ **I am less active because of my breathing difficulties**
- ☐ **I am less active for other reasons:**
- ☐ **I am more active**

What sport: ____

What level: ☐ **exercise** ☐ **local club** ☐ **regional** ☐ **national** ☐ **international**

Please make a mark on the line, on a score from 0-10, how you experienced your difficulties
<u>when you took the treadmill test:</u>

No problem **0---10** **Worst of all possible**

Please make a mark on the line, on a score from 0-10, how you experience your difficulties
<u>now</u>:

No problem **0---10** **Worst of all possible**

What has happened since the examination?
- ☐ **I now have no symptoms of breathing difficulties during exertion**
- ☐ **The symptoms of breathing difficulties are unchanged**
- ☐ **The symptoms of breathing difficulties are better**
- ☐ **The symptoms of breathing difficulties have become worse**

Do you use any asthma medication now?
- ☐ **no, I don't use any asthma-medication**
- ☐ **yes, because of breathing difficulties during exertion**

If yes, does this work? ☐ **yes** ☐ **I don't know, but I use asthma medication anyway**

What type of medication?
- ☐ **To open the airways (for instance: Ventolin, Bricanyl, ---**
- ☐ **To prevent difficulties (for instance Flutide,…**

Have you used asthma medication before? ☐ **no** ☐ **yes: what kind?**________________________

Did it help? ☐ **yes** ☐ **no** ☐ **I don't know**

Please circle the statement that fits best for you;

1 never, 2 some times, 3 often, 4 almost always, 5 every time

My breathing difficulties have been a psychological strain	1	2	3	4	5
The difficulties have led to less social interaction	1	2	3	4	5
The difficulties have made me feel sad	1	2	3	4	5
The difficulties have kept me from achieving what I wanted	1	2	3	4	5

Below follow questions that you have previously answered in connection with the examination, if you still have difficulties we ask that you please answer them again.

How afflicted are you currently:

- ☐ **not at all**
- ☐ **slightly**
- ☐ **a great deal**
- ☐ **extremely**
- ☐ **to the degree of disability**

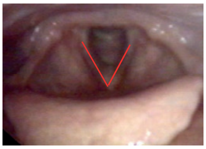
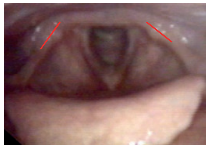
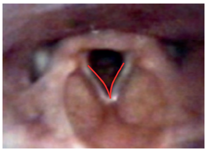
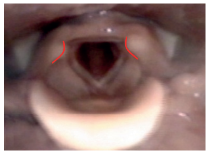
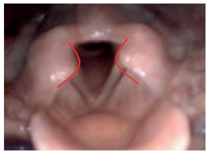
How often do your breathing difficulties currently occur in connection with exertion, please circle the statement that fits best for you:

1 = never
2 = sometimes
3 = often
4 = almost always
5 = every time (or constant)

	Answer code 'mark with O'				
I have breathing difficulties when I am at rest	1	2	3	4	5
I get breathing difficulties during physical activity	1	2	3	4	5
I hear noise/squeaky sounds from my airways when I am doing physical activities	1	2	3	4	5
My breathing difficulties prevent me from exercising	1	2	3	4	5
I get frightened when the breathing difficulties occur	1	2	3	4	5
I tend to not push myself physically because of my breathing difficulties	1	2	3	4	5
The breathing difficulties continue even after I stopped / rest after exertion	1	2	3	4	5

Please return this form in the enclosed envelope, thank you for taking the time to respond!

EILO grading system

	Glottic Grading of parameters A and C:		***Supraglottic*** Grading of parameters B and D:	
Evaluation of the laryngoscopy video recording:* Glottic / Supraglottic A | B C | D	Expected maximal abduction of the vocal cords (normal) 	**0**	Expected maximal abduction of the aryepiglottic folds with no visible medial rotation (tops of cuneiform tubercles pointed vertical or slightly lateral) 	**0**
	Narrowing or adduction anteriorly of rima glottidis without visible motion of the arytenoid cartilage synchronised to inhalation. 	**1**	Visible medial rotation of the cranial edge of the ary-epiglottic folds and tops of the cuneiform tubercles (synchronous to inhalation). 	**1**
Sum score: **E= A+B+C+D** Clustered Sum score:	Inhalation synchronised adduction of vocal cords but no contact between cords. 	**2**	Further medial rotation of the cuneiform tubercles with exposure of the mucosa on the lateral side of the tubercles (synchronous to inhalation). 	**2**
- I: E = 0,1,2 **- II: E = 3,4** **- III: E = ≥ 5**	Total closure of the glottic space synchronous to inhalation 	**3**	Medial rotation until near horizontal position of the cuneiform tubercles and tops of the cuneiform tubercles moves towards the midline (synchronous to inhalation). 	**3**
Moderate effort Scores:	**A**	0 1 2 3	**B**	0 1 2 3
Maximal effort Scores:	**C**	0 1 2 3	**D**	0 1 2 3

*The scores at each level (*glottic* (A and C) and *supraglottic* (B and D)) were assessed at moderate (A,B) (when subject started to run) and at maximal effort (C,D) (just before the subject stopped running at the treadmill); all four numbers (A-D) were noted together with a sum score (E) for each test/subject.