Larynx in exercising humans

The unexplored bottleneck of the airways

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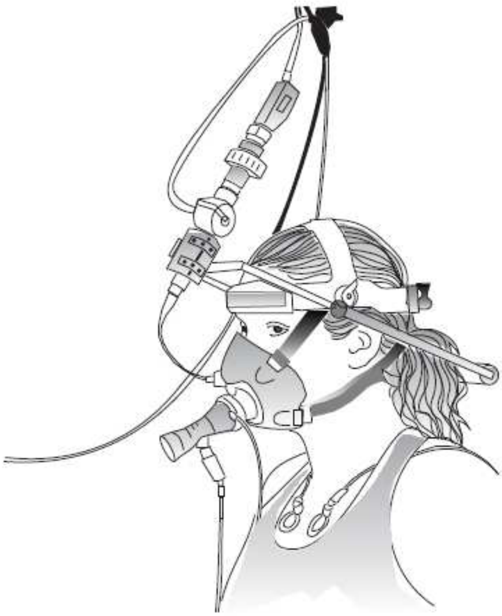

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1. Acknowledgements

The curiosity and the interest which forms the basis for this thesis has its origin in the experiences I gained as a physiotherapist at Geilomo Childrens Hospital. I would therefore like to thank all my former colleagues and patients at Geilomo Childrens Hospital. They all contributed to a sincere interest in the work with children and young people suffering from breathing problems and made this into a life long project. Particularly, I owe much to the late Svein Oseid and to Kai-Håkon Carlsen, Terje Sandnes and Frode Njå who taught me the clinical aspects of asthma and formed my critical thinking, so important for academic work.

In 1997, I moved to Bergen and started as the head of the Pediatric Cardiopulmonary Test Laboratory at Haukeland University Hospital. There I met colleagues who shared my curiosity regarding what really happens in the throat of people with exercise-induced inspiratory breathing difficulties. My supervisor Thomas Halvorsen has been my most important motivator and supporter. Thanks to him, my daily work at the test laboratory has been challenging and interesting. I have found answers to some questions, and it has been a pleasure to go to work. As long as unresolved questions remain, the at times loud discussions between us will continue.

With Britt Skadberg and John-Helge Heimdal joining the group, we eventually became a "club of four", and the upper airway group at Haukeland University Hospital was established as a joint venture between the ENT and Pediatric departments. A milestone in this cooperation was when we first managed to make video and sound recordings from the larynx during ongoing maximal treadmill exercise. The method was published under the name "Continuous Laryngoscopy Exercise Test" (CLE-test) in Laryngoscope in 2006, and forms the foundation for this thesis.

I particularly want to thank my two supervisors Thomas Halvorsen and John-Helge Heimdal for enthusiastic discussions and for the effort they have put into this work. They both have the ability to see opportunities instead of restrictions. Britt Skadberg did a fantastic job to systematize our work in the early years. After she left us for administrative work, she has been of vital importance for facilitating good working and operating conditions at the Pediatric Department. A huge thank must be given to Jan Olofsson who in his role as laryngologist and director of the ENT Department has supported the project and been a catalyst over several areas. I am also indebted to the engineers Rune Økland and Terje Haaland. Their enthusiasm and expertise was important for making the CLE- test possible. Thanks also to the Centre for clinical research at Haukeland University Hospital for financial support and statistical guidance and to Innovest for financial support.

Robert Maat became a good friend and a central collaborator. He joined the group after the CLE-test had been established. Over the years, Robert and I have spent hours of together, studying and discussing the various throat responses to exercise. Robert helped developing this project, and contributed to a better understanding, better diagnostics and better treatment of patients with inspiratory breathing difficulties during exercise. Photographer Tor Andre Ellingsen at the ENT Department has been invaluable to ensure high quality video and sound recordings as well as in the work of editing the recordings. During the last years of the project, Lorentz Sandvik and Magnus Hilland have made important contributions. Through co-operating with these young men, I see a bright future for the project.

I will also take this opportunity to thank those who have been at home while I had fun at work, namely my dear family. Thanks to Ann-Helen, Daniel, Birgitte, Håvard and Amalie who made it so nice to come home, and thanks for the patience you have shown, when I have spent slightly too much time at work.

Finally, I thank all the colleagues I have worked with over the years. I have learned a lot from you, both you at Geilomo Childrens Hospital and Haukeland University Hospital. A special thanks to the Pediatric Department and its chief executives, Robert Bjerknes and Britt Skadberg, who have given me the opportunity to work with something I am really passionate about.

2. Abbreviations

ACCP	American College of Chest Physicians
AEF	Aryepiglottic Fold
ANOVA	Analysis of Variance
BPD	Broncho Pulmonal Dysplacia
CLE-test	Continiuous Laryngoscopy Exercise test
EELV	End-Expiratory Lung Volume
EIA	Exercise Induced Asthma
EIIS	Exercise Induced Inspiratory Stridor
EIL	Exercise Induced Laryngomalacia
EILV	End-Inspiratory Lung Volume
EILD	Exercise Induced Laryngeal Dysfunction
EILO	Exercise Induced Laryngeal Obstruction
EI-VCD	Exercise Induced Vocal Cord Dysfunction
ELS	European Laryngological Society
ENT	Ear Nose Throat
EP	Extremely Preterm
ERS	European Respiratory Society
extFVLs	Exercise tidal Flow Volume Loops
FEV_1	Forced Expiratory Flow in the first second
FVC	Forced Vital Capacity
FVL	Flow Volume Loop
GERD	Gastro Esophageal Reflux Disease
IMST	Inspiratory Muscle Strength Training
IS	Inspiratory Stridor
LPR	Laryngopharyngeal Reflux
LVCP	Left Vocal Cord Paralysis
MEF	Maximal Expiratory Flow
MFVL	Maximal Flow Volume Loop
MIF	Maximal Inspiratory Flow

MMV	Maximal Minute Ventilation calculated
MVE	Maximal Minute Ventilation
NSD	Norsk Samfunnsvitenskapelige Datatjeneste
PCA	Posterior Crico-Arytenoid
PDA	Patent Ductus Arteriosus
PFT	Pulmonary Function Test
PND	Post Nasal Drip
POLO	Periodic occurrence of laryngeal obstruction
PPI	Proton Pump Inhibitor
PVFM	Paradoxical Vocal Fold Motion
PVCM	Paradoxical Vocal Cord Motion
RSI	Reflux Symptom Index
RV	Residual Volume
RQ	Respiration Quotient
SD	Standard Deviation
TLC	Total Lung Capacity
VAS	Visual Analogue Scale
VCD	Vocal Cord Dysfunction
PeakVO_2	Peak Oxygen uptake

3. Summary

Exercise induced dyspnoea is not unusual in young and otherwise healthy individuals. Based on the presenting symptoms alone, it may be challenging to differentiate exercise induced asthma from exercise related obstruction of central airways. This may lead to diagnostic confusion and inappropriate treatment. Central airway obstruction usually presents with inspiratory symptoms during ongoing exercise, often labelled exercise induced inspiratory stridor (EIIS). EIIS typically peaks towards the end of the exercise session while the expiratory symptoms of EIA typically peak after exercise has stopped.

Until now, laryngeal function during ongoing exercise in symptomatic individuals has hardly been visualised. Furthermore, the taxonomy of this area is confusing. A range of different terms have been used to label clinical scenarios that may appear relatively similar. Additionally, very specific anatomical terms, such as vocal cord dysfunction (VCD), have been used to label symptoms that may be related to different abnormalities. This situation is unfortunate for the understanding of EIIS, and it precludes individualised treatment of patients.

AIMS OF THE STUDY

(1) To develop a method for continuous video recorded laryngoscopy during ongoing heavy treadmill exercise, with simultaneous external video and audio recordings.

(2) To apply this method in an observational study design, with the purpose to explore laryngeal response pattern(s) to exercise in a large group of patients presenting with symptoms of EIIS, and in control subjects with no such symptoms.

(3) To use this method to grade and characterise exercise induced laryngeal obstruction (EILO), and to investigate its progression during increasing ventilatory requirements throughout a maximal exercise test.

(4) To assess reliability and validity of the observations made.

DESIGN. Descriptive, observational, cross-sectional, controlled clinical study.

SUBJECTS. In papers # 1, # 2 and # 3, patients with EIIS were consecutively recruited from the outpatient pulmonology clinic at the Pediatric Department, Haukeland University Hospital over a period of six year (2002 – 2007). In paper # 4, subjects born extremely preterm in the period 1982-85 who had a neonatal history of surgical closure of a patent ductus arteriosus (PDA), were examined for left sided vocal cord paralysis.

METHODS. Video recorded Continuous Laryngoscopy Exercise (CLE) test was performed in parallel with continuous video recordings of the upper part of the body and recordings of breath sounds, in subjects running to respiratory distress or to exhaustion on a treadmill. A score system was developed, grading and characterizing laryngeal obstruction, according to a predefined manual.

RESULTS.

Paper # 1. The CLE-test was feasible, the test situation was well tolerated, and the presenting symptoms of respiratory distress could be reproduced in most patients. The CLE-test could provide visual information on laryngeal response patterns during increasing ventilatory requirements, imposed by incrementing exercise.

Paper # 2. Larynx can safely be studied with laryngoscopy throughout maximum intensity treadmill exercise in children and young adults. In most patients, the sense of dyspnoea seemed to coincide with a prolonged inspirium, accompanied by gradually increasing coarse breath sounds. In parallel, a medial rotation of the cuneiform tubercles and subsequent anteromedial movement of aryepiglottic folds were observed in the majority of patients. Vocal cord adduction was usually observed secondary to supraglottic adduction. We were unable to link symptoms of EIIS to one single factor.

Paper # 3. The score system differentiated patients from control subjects. The correlation between CLE-test sum scores and symptom scores was adequate. Inter and intra-observer consistencies were moderate to good.

Paper # 4. Seven (54%) out of 13 subjects born extremely preterm and exposed to neonatal surgical closure of a PDA had left vocal cord paralysis (LVCP). Subjects with LVCP had significant airway obstruction but no decreases in aerobic capacity. The CLE-test revealed increasing respiratory symptoms in parallel with increasing anteromedial collapse of the left aryepiglottic folds as the exercise increased. None of these patients had been correctly diagnosed before entering the present study. Most had erroneously been assigned other diagnoses.

CONCLUSION. Laryngoscopy can safely be performed throughout maximum intensity treadmill exercise in children and young adults with and without exercise related respiratory symptoms. The laryngeal response patterns may be described and scored with adequate reliability. Seemingly similar symptoms may be related to a variety of abnormalities of central airways. Laryngoscopy during ongoing exercise is required to appreciate this complexity. At present, no diagnostic labelling should be performed and no treatment regimes should be instituted for this clinical scenario without endoscopic documentation.

4. List of publications

1. Heimdal JH, Røksund OD, Halvorsen T, Skadberg BT, Olofsson J. Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise. Laryngoscope 2006; 116(1):52-57

2 Røksund OD, Maat RC, Heimdal JH, Olofsson J, Skadberg BT, Halvorsen T. Exercise induced dyspnoea in the young. Larynx as the bottleneck of the airways. Respir Med. 2009 Dec;103(12):1911-8.

3 Maat RC, Røksund OD, Halvorsen T, Skadberg BT, Olofsson J, Ellingsen TA, Aarstad HJ, Heimdal JH. Audiovisual assessment of exercise-induced laryngeal obstruction: Reliability and validity of observations. Eur Arch Otorhinolaryngol. 2009 Dec;266(12):1929-36.

4. Røksund OD, Clemm H, Heimdal JH, Aukland SM, Sandvik L, Halvorsen T. Left vocal cord paralysis after extreme preterm birth, a new clinical scenario in adults. Pediatrics. 2010 Dec;126(6):e1569-77. Epub 2010 Nov 22.

5. Background information

5.1 Personal introduction.

Exercise induced dyspnoea is a common complaint among adolescents and young adults. Symptoms are often caused by exercise induced asthma (EIA) or by obstruction of the central airways (Goldman 1997; Lakin et al. 1984; Weinberger & Abu-Hasan 2007). Clinically and based on symptoms alone, these entities may be difficult to differentiate. Central airway obstruction usually present as dyspnoea during ongoing exercise, often described as exercise induced inspiratory stridor (EIIS). This clinical scenario is recognized by high-pitched inspiratory noise, shortness of breath, throat tightness and occasionally panic reactions (Christopher et al. 1983; Rundell & Spiering 2003). EIIS typically peak towards the end of an exercise session and during the first 2-3 minutes of recovery (Christopher & Morris 2010; Morris & Christopher 2010), contrary to the expiratory symptoms of EIA, typically peaking 3-15 minutes after the exercise has stopped (Anderson et al. 1975).

Authors tend to assign symptoms of EIIS to diagnostic entities that point at abnormalities or dysfunctions of particular structures of the central airways, most often to the vocal cords. Thus, the term vocal cord dysfunction (VCD) is a diagnostic term that is often used. However, in most of the literature in this area, diagnoses have not been confirmed with objective test methods (McFadden, Jr. & Zawadski 1996; Rundell & Spiering 2003; Vlahakis et al. 2002). The same applies for causal mechanisms; various explanatory theories are proposed without having performed the studies that are necessary to demonstrate such causal relationships. Given the complex nature of the central airways, heterogeneity of findings is to be expected in patients with EIIS. Diagnostic heterogeneity requires a clear strategy for diagnostic investigations. Furthermore, therapeutic measures should be based on findings in the individual patient.

Several authors have proposed that flexible transnasal fiberoptic laryngoscopy performed during ongoing symptoms should be the diagnostic gold standard in patients with EIIS (Beaty et al. 1999; Christopher et al. 1983; Ibrahim et al. 2007; Smith et al. 1995; Spanos et al. 2009). However, until now this has rarely been done during ongoing exercise in the studies that have been published.

Geilomo Childrens Hospital is a traditional mountain hospital, focusing on habilitation of children with asthma referred from all over Norway. Working there from 1986-1997, I noticed that some patients had exercise induced shortness of breath that did not fit the typical pattern seen with exercise induced asthma. In addition, they did not seem to respond as expected to asthma treatment. Diagnostic considerations and literature search suggested the diagnosis exercise-induced vocal cord dysfunction (EI-VCD). However, there were no diagnostic methods available to verify this diagnostic entity. In 1998, the ”Upper Airway Group” was established at Haukeland University Hospital as a collaboration between the Ear Nose Throat (ENT) and the Pediatric departments. The group consisted of Jan Olofsson and John-Helge Heimdal from the ENT Department and Britt Torunn Skadberg, Thomas Halvorsen and myself from the Pediatric Department. The explicit goal of this collaboration was to develop better diagnostic methods for patients with EIIS. Initially, patients were examined with laryngoscopy after the exercise had been stopped, while they were still symptomatic. Difficulties introducing the laryngoscope in patients with panic and a high rate of negative tests became apparent at an early stage. Additionally, post-exercise laryngoscopy gave no information regarding what had incited the laryngeal obstruction, as the response was already present when the endoscope was introduced. Several years of doing and failing led to the development in 2002 of the method that forms the basis for the work of this thesis, the Continuous Laryngoscopy Exercise test (the CLE-test), facilitating video recorded laryngoscopy throughout a full maximal exercise test.

This thesis summarises the diagnostic considerations and the methodology applied over the past ten years working with patients suffering from EIIS. In the four papers, the role played by the larynx as the “bottleneck of the airways” and the great variation of the laryngeal response patterns to exercise, is being emphasized. The importance of alternative diagnoses is being highlighted with examples, such as exercise induced asthma and paralysis of the left recurrent laryngeal nerve.

5.2 Historical overview regarding laryngeal obstruction

In 1842, Dunglison was the first to describe Periodic Occurrence of Laryngeal Obstruction (POLO) associated with dyspnoea and noisy breathing (Dunglison 1842). He described a disorder in "hysteric females" that he termed hysterical croup. Flint noted a similar phenomenon in two male adults and named it laryngismus stridulus (Flint 1842). MacKenzie (1869) was the first to report evidence of abnormal vocal fold movements documented by laryngoscopy (MacKenzie 1869), describing paradoxical closure of the vocal folds during inspiration in hysteric patients. In the 1902 edition of "The principles and practise of medicine", William Osler (Osler W 1902) described "Spasms of the muscles may occur with violent inspiratory efforts and great distress, and may even lead to cyanosis. Extraordinary cries may be produced, either inspiratory or expiratory". Little new was published on this phenomenon until the 1970s when Patterson and colleagues described a condition they called Munchausen's stridor (Patterson et al. 1974). In 1984, Lakin and colleagues were the first to describe inspiratory prolapse of the corniculate and cuneiform cartilages of the aryepiglottic folds narrowing the supraglottic opening (Lakin et al. 1984).

5.3 Periodic Occurrence of Laryngeal Obstruction (POLO)

In 2010, Christopher et al proposed that the phrase POLO should serve as an overarching term (Christopher & Morris 2010), covering all conditions caused by abnormal movements of glottic or supraglottic structures. They suggested that it could be split into three categories based on the triggering factor(s), i.e. psychogenic, exertional and irritant induced. The symptoms of the subcategories are often similar and consist mainly of noisy breathing, prolonged inspiration, inspiratory stridor (IS) and sometimes panic reactions (Rundell & Spiering 2003). In this thesis I will concentrate on the exertional category, i.e. central airway obstruction presenting as inspiratory dyspnoea and stridor triggered mainly by exercise. Although proper stridor is not always present, these symptoms are often described collectively as exercise induced inspiratory stridor (EIIS) (Christopher & Morris 2010; Morris & Christopher 2010; Rundell & Spiering 2003).

5.3.1 Confusion regarding the nomenclature

The focus on the phenomenon of POLO has increased over the past 40 years, and more than 70 new and different terms have been linked to its description (Brugman 2009). It has for some time been recognized that symptoms resembling EIIS may be related to more than one abnormality of the central airways; however, most authors have applied their terminology as if EIIS is related to only one diagnostic entity. The most well known examples of terms that have been applied over the years, are vocal cord dysfunction (VCD) (Christopher et al. 1983), pardoxical vocal fold motion (PVFM) (Patel et al. 2004), paroxysmal vocal cord dysfunction (PVCM)(Kellman & Leopold 1982), irritable larynx syndrome (Morrison et al. 1999), functional upper airway obstruction (Appelblatt & Baker 1981), exercise-induced laryngochalasia (Bjornsdottir et al. 2000), exercise-induced laryngomalacia (Bent, III et al. 1996; Mandell & Arjmand 2003; Smith et al. 1995) and late onset laryngomalacia (Gessler et al. 2002). These examples of terminology indicate that the authors seem to have clear opinions regarding the anatomical structures and the causal mechanisms that are involved, and that EIIS should be understood within one specific conceptual framework. However, the opinions expressed are in most articles based on symptom presentation alone, unsubstantiated by visual or objective test methods that demonstrate actual findings. The critical question is whether the conditions described do in fact represent what the labels suggest or if the terminology merely reflects the diagnostic approaches and a'priori points of view, held by the authors.

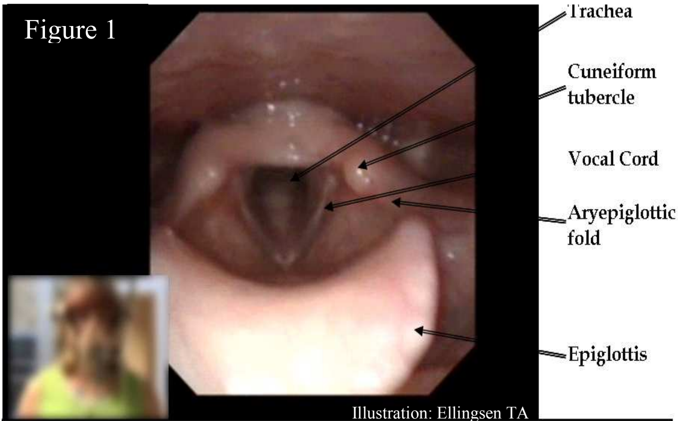
The terms most frequently encountered in the literature and used extensively in clinical practise are vocal cord dysfunction (VCD) (Christopher et al. 1983) or paradoxical vocal fold motion (PVFM) (Patel et al. 2004). Otolaryngologists and speech pathologists are most likely to use PVFM while pulmonologists, allergists, psychiatrists and psychologists generally prefers to use the term VCD (Christopher & Morris 2010). Since VCD and PVFM are difficult to differentiate from each other, VCD will be used in this thesis to cover both.

Smith and co-workers were the first to identify supraglottic obstruction in patients with EIIS, later, described also by others (Beaty et al. 1999; Bent, III et al. 1996; Bjornsdottir et al. 2000; Fahey et al. 2005; Gessler et al. 2002; Mandell & Arjmand 2003; Smith et al. 1995). They called the phenomenon exercise induced laryngomalacia (EIL). The most common anatomic description of EIL are anteromedial prolapse of the arytenoids or the epiglottis being drawn backward acting as a lid (Bent, III et al. 1996). If exercise induced supraglottic and glottic laryngeal obstruction share a common pathophysiology has not been determined.

The original description of vocal cord dysfunction (VCD) was “a disorder presenting as asthma and described endoscopically as wheeze due to adduction of the true and false vocal cords throughout the respiratory cycle; the glottis narrowed to a small posterior diamond-shaped chink” (Christopher et al. 1983). Unfortunately, it seems that VCD have unintentionally become a term used to describe several other clinical presentations of inspiratory stridor. Further increasing the confusion, authors have proposed new definitions for VCD. Brugman proposed that since the term VCD had been used most often in the literature to denote a functional laryngeal complaint, it should be used as a standard for our understanding and reporting of this disorder (Brugman 2009). Her proposed definition was “VCD is a spectrum of nonorganic disorders involving the larynx and/or periglottic structures. Acute upper airway obstruction occurs when the vocal cords close paradoxically on inspiration and/or the supraglottic structures prolapse or constricts” (Brugman 2009). Kenn and Balkisson suggested that “VCD is an intermittent extrathoracic airway obstruction, occuring mainly during inspiration and leading to dyspnoea of varying intensity” (Kenn & Balkissoon 2011).

In our research group, we used for years the umbrella term Exercise Induced Laryngeal dysfunction (EILD) to describe supraglottic as well as glottic laryngeal obstruction presented during exercise. Based on a Scandinavian initiative, the issue of terminology in relation to POLO has been addressed by the European Laryngological Society (ELS) and the European Respiratory Society (ERS). A joint ELS/ERS Task Force was appointed by the ERS in 2010, with subsequent representation also from the American College of Chest Physicians (ACCP), with the directive to develop guidelines for taxonomy.

Based on a preliminary Scandinavian agreement, and in anticipation of final guidelines from the ELS/ERS/ACCP Task Force, the term Exercise Induced Laryngeal Obstruction (EILO) will be used in this thesis. EILO may be split into a glottic form, involving the vocal cords and the false vocal cords, and supraglottic form, involving the cuneiform tubercles, the aryepiglottic folds and maybe also the epiglottis. A combination of these two forms may also be observed (Figure 1).



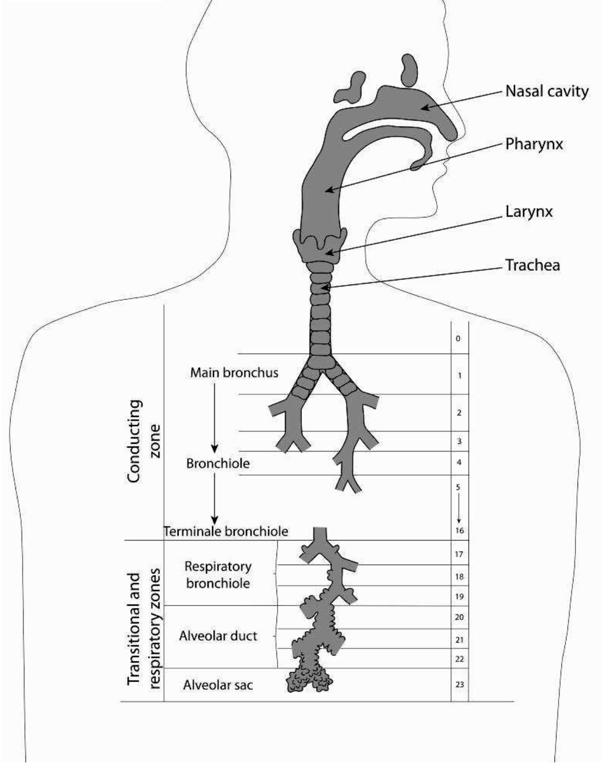
Normal larynx, as observed transnasally in a flexible laryngoscope, with the patient in the lower left corner (anonymised). Epiglottis (at front), the cuneiform tubercles and the aryepiglottic folds represent supraglottic structures. The vocal cords (glottis) and the upper part of the trachea are seen below

5.4 The structure and the physiology of the Airways

Air enters the nose and the mouth before flowing into the conductive part of the ventilatory system (Figure 2). The air is warmed, filtered and almost completely humidified as it passes through the irregular surfaces found inside the nose. From the nose and mouth the air passes through the pharynx, larynx, trachea, bronchi and bronchioles until it reaches the alveoli and the gas exchanging units of the lung (McArdle et al. 1995).

5.4.1 The ventilatory system

Figure 2



The ventilatory system. Illustration: Ellingsen TA.

The ventilatory system consists of two parts: a conducting zone and the respiratory zone. Air is brought into the lungs by bulk flow, driven by the negative intrathoracic pressure caused by the action of the respiratory muscles. However, when air reaches the terminal bronchioles, the large increase in the cross sectional area changes distribution to diffusion, which is also the mode by which the gases are distributed across the alveolar-capillary membrane (McArdle et al. 1995).

Inspiration is an active process involving the diaphragm and the external intercostal muscles. The external intercostal muscles make the ribs swing up and out and the sternum to swing up and forward. At the same time, the diaphragm contracts, flattening down towards the abdomen. These actions expand the thoracic cage, reducing the intrapulmonary pressure. Because the respiratory tract is open to the outside, air flows into the lungs. During exercise, inspiration is further assisted by the action from other muscles, such as the scalene and sternocleidomastoid in the neck and the pectorals in the chest.

Expiration is in healthy subjects at rest a passive process, driven by the elastic recoil of the lung tissue. As the diaphragm relaxes, it returns to its normal upward and domed position. As the external intercostal muscles relaxes, the ribs and sternum lower back into their resting positions. While this happens, the elastic property of the lung tissue causes it to recoil to its resting size, squeezing the air out of the lungs. During exercise, expiration becomes a more active process. The internal intercostal muscles can actively pull the ribs down, assisted by the muscles latissimus dorsi and the quadratus lumborum. Contraction of the abdominal muscles may accelerate the return of the diaphragm to the domed position (McArdle et al. 1995; Wilmore & Costill 1999).

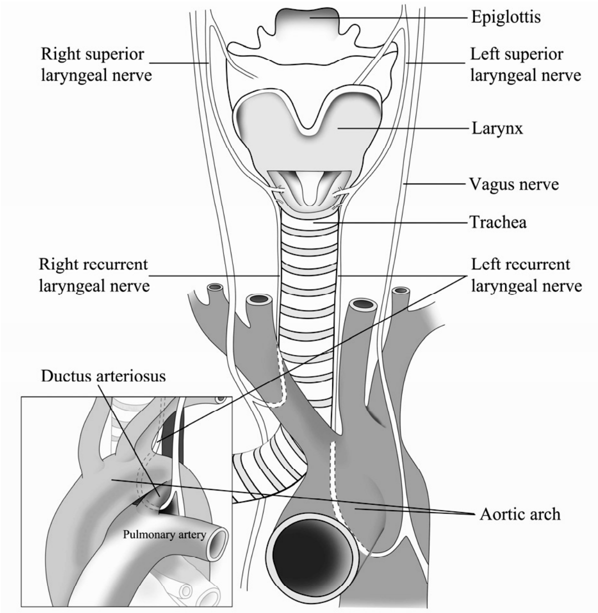
5.4.2 The anatomy and the function of the larynx

The larynx serves to protect the lower airways, facilitates respiration, and plays a key role in phonation. The protective function is entirely reflexive and involuntary, whereas the respiratory and phonatory functions are initiated voluntarily but regulated involuntarily.

The larynx extends vertically from the tip of the epiglottis to the inferior border of the cricoid cartilage. The laryngeal interior can be divided into supraglottic, glottic and subglottic levels.

The epiglottis projects obliquely up behind the tongue and represents the anterior border of the laryngeal inlet. From the lateral margin of the epiglottis the aryepiglottic folds extend backwards and medially and make a nearly circularly formed margin of the laryngeal inlet. Dorsally, both aryepiglottic folds are separated by the intra arytenoid notch. The posterior part of each aryepiglottic folds are bulged by the corniculate and cuneiform cartilages (Reidenbach 1998).

Figure 3



The anatomy of larynx and relevant vascular structures and nerves. Illustration: Ellingsen TA

The scaffold of the larynx is the cricoid cartilage which is the only circular cartilage of the airway. It represents the lower border of the larynx and is anchoraged to the trachea. Above the cricoid cartilage, the thyroid cartilage represents the anterior stabilisation of the larynx. Motion between these cartilages regulates the tension and length of the vocal cords. Posteriorly, on top of the cricoid plate, there are two small joints on which the arytenoid cartilages are positioned. These triangular shaped cartilages facilitate abduction and adduction of the vocal cords. The motion of the arytenoids is mainly regulated by the arytenoids muscles that are stretching between the cartilages with oblige and horizontal bellies. The abduction and adduction of the vocal cords is further regulated by the lateral and posterior crico-arytenoid (PCA) muscles, respectively. The latter (PCA) muscle is capable of separating the vocal cords. If this muscle is incapacitated on one or both sides, the patient is unable to pull the vocal cords apart which may cause airway obstruction and stridor.

Sensory nerves to the larynx are derived from the internal branch of the superior laryngeal nerve and the recurrent laryngeal nerves; both branches of the vagus nerve (Figure 3). The internal branch of the superior laryngeal nerve and the recurrent laryngeal nerves innervate the mucosa above and below the level of the true vocal cord, respectively. The recurrent laryngeal nerve innervates all intrinsic laryngeal muscles except the crico-thyroideus muscle, which is innervated by the external division of the superior laryngeal nerve. The left recurrent laryngeal nerve is intimately related to the aorta and the ductus arteriosus. This close relation makes the nerve vulnerable to damage during surgical treatment of a patent ductus arteriosus (PDA).

During swallowing, the larynx is elevated to let food pass into the oesophagus, and tightly closed by the laryngeal sphincter mechanism. Reflexive glottic closure is achieved by simultaneous adduction of both vocal cords. Laryngeal denervation may lead to aspiration during swallowing.

Closure of the larynx facilitates the ability of increasing intra-thoracic or intra-abdominal pressure in cough, vomiting, defecation, urination, parturition, and thoracic fixation during strenuous work with upper limbs.

The respiratory movements of the vocal cords are closely co-ordinated with those of the diaphragm and the other muscles of ventilation. There is a phasic relationship between the activity of the diaphragm and the PCA muscle. During inspiration, the activity of the PCA muscle occurs slightly before the diaphragm, and continues its contraction to mid-inspiration. This is a very consistent and reproducible pattern that may be observed across many subjects (Brancatisano et al. 1984). This phasic relationship suggests that when the stimulation of the diaphragm is increased, the PCA activity increases in a co-ordinated manner, creating a synergistic effect (Van et al. 1983). The laryngeal valve mechanism can precisely regulate the trans-glottic pressure difference and thereby the resistance to flow. This phased vocal fold movement may contribute to the maintenance of the alveolar patency of the lungs by providing positive airway pressure during expiration (Koufman & Block 2008; Mathers-Schmidt & Brilla 2005).

5.4.3 Laryngeal function during increasing work

At rest, the glottis normally narrows during expiration and opens during inspiration (Brancatisano et al. 1983). During exercise, the epiglottis tilts forward and the aryepiglottic fold are lengthened and thinned at the laryngeal inlet (Belmont &

Grundfast 1984). At the glottic level of the laryngeal lumen, the cross-sectional area is increased by elongation and abduction of the vocal cords. This motion is due to the activity of intrinsic muscles, particularly the PCA (England & Bartlett, Jr. 1982; Hurbis & Schild 1991). These adaptive changes can reduce the increases of turbulence and of airway resistance that would otherwise have occurred. This assumption is supported by Ferris et al (Ferris et al. 1964), who demonstrated that while airflow increases from 0.4 litre/sec to approximately 1 litre/sec, the laryngeal component of total pulmonary resistance increases from 12% to 26%.

Bent et al. visualized by continuous laryngoscopy the adaptation of the larynx to exercise in 10 healthy subjects (Bent, III et al. 1996), and confirmed the observations of two previous reports (England & Bartlett, Jr. 1982; Hurbis & Schild 1991). In most subjects (80%), the epiglottis rotated anteriorly towards the tongue base. In two subjects, a slight prolapse of the corniculate cartilages into the posterior glottis was observed with inspiration. In the remaining eight subjects, the posterior supraglottic support was maintained. The authors speculated that these subjects had more effective muscular support, better neuromuscular tone during exercise, a greater absolute cross-sectional area of the airway or a combination of these factors (Bent, III et al. 1996; Rundell & Spiering 2003).

5.5 Dyspnoea during exercise

Pulmonary ventilation increases during exercise, induced by the increasing metabolic demands of the body. At low intensity exercise, increased ventilation is accomplished mainly by increased tidal volumes, while at higher intensities, the rate of respiration also increases (Hurbis & Schild 1991; Wilmore & Costill 1999). In elite athletes, there have been measured maximal minute ventilation values of 280 litres per minute (Carlsen & Kowalski 2008; Hurbis & Schild 1991). At low intensity exercise, much of the ventilation may take place through the nose, but as the intensity increases there is a transition from nasal to mouth breathing. This change usually occurs when minute ventilation reaches 25-30 litres per minute (Ferris et al. 1964; Hurbis & Schild

1991). Active opening of the mouth tends to widen the laryngeal opening (Fink BR 1975).

5.5.1 Exercise induced breathlessness

Ideally, during exercise, breathing is regulated in a way that maximizes the ability to perform. Unfortunately, this does not always happen, and a variety of respiratory problems can thereby limit performance. The most common cause of poor performance is poor physical fitness, but different diseases, structural airway abnormalities, poor breathing techniques or psychological causes are other possible explanations. A well described disease, often relevant to young people in this context is exercise induced asthma (EIA). EIA is present in 8-10% of an unselected childhood population, and in ~ 35% children with asthma (Carlsen 2011). In athletes, EIA has been reported in 20–50% (Rundell et al. 2001; Rundell & Spiering 2003; Voy 1986; Weiler & Ryan, III 2000; Weiler et al. 2007). Obstruction of the upper airways is another cause of exercise related breathlessness. The prevalence of exercise induced laryngeal obstruction (EILO) was 7.5% in an unselected cohort of adolescents and young adults from Copenhagen (Christensen et al. 2011). Inspiratory stridor (IS) was observed in 5.1% of athletes who volunteered to undergo routine evaluation for asthma or EIA at the US Olympic Training centre in Lake Placid. IS was more prevalent in outdoor athletes (8.3%) compared to indoor athletes (2.5%) (Rundell & Spiering 2003). This finding suggests that environmental stimuli may be involved in the pathogenesis of EILO, as is also demonstrated for EIA. In subjects with EIA-like symptoms, asthma could be verified in only ~ 50% (Rice et al. 1985; Rundell & Spiering 2003), and the diagnosis of asthma was incorrect in ~ 30% (Aaron et al. 2008; Rundell & Spiering 2003).

5.6 Diagnostics of exercise induced laryngeal dyspnoea

Diagnostic tests should identify or rule out diagnoses. A diagnostic test should turn out (positive) when someone is diseased, and should not turn out (negative) when someone is healthy. To validate a test, it must be compared with some reference, identifying the condition in question with some degree of accuracy (the best test available on the site), a so-called ”gold standard”.

There are very few diagnostic tests that turn out positive in all diseased individuals and negative in all healthy individuals. The diagnostic sensitivity of a test, describes the ability of the test to identify diseased individuals (optimally as close to 100% as possible), while the specificity describes ability of the test to exclude healthy individuals (optimally as close to 100% as possible). Positive predicted value is the ratio of individuals with a positive test who actually have the disease, while negative predicted value is the ratio of healthy individuals who are correctly identified with a negative test. The predicted value of a positive or negative test-outcome is influenced by the prevalence of the disease in the population under study. The more uncommon the disease is, the more likely a negative result indicates absence of disease and the less likely a positive result really indicates disease. Since the prevalence may not be known or vary between populations, we should not take the predictive values observed in any given study as applying universally (Altman 1995).

Biological characteristics are mostly distributed along a continuous scale where the disease represents an extreme. It is often challenging to define exactly how and why at this scale the normal ceases and disease begins. For each possible threshold-value one chooses, there will be some diseased who are correctly classified with a positive test (true positive), but some diseased who are incorrectly classified with a negative test (false negative). The same applies to the healthy; some will be correctly classified with a negative test (true negative) while some will be incorrectly classified as diseased with a positive test (false positive). Changing the threshold for a positive test will influence the distribution of false and true positive and negative results. Validated, reliable and objective test methods are necessary in the difficult and necessary work of mapping this boundary point. Often, disease concepts are adapted to the information provided by such test methods (Altman 1995).

Three main criteria have been proposed to establish the diagnosis of EILO (Christopher & Morris 2010; Fahey et al. 2005; McFadden, Jr. & Zawadski 1996; Rundell & Spiering 2003; Tervonen et al. 2009): (1) Clinical symptoms of exercise induced inspiratory stridor. (2) Confirmatory pulmonary function findings. (3) Laryngoscopic evidence of EILO. The clinical and laryngoscopic criteria are proposed as absolutely essential, whereas pulmonary function test findings are not.

Regarding these proposed criteria, the work required to define the boundaries between normal and abnormal in order to distinguish diseased from the healthy, have only just begun.

5.6.1 Clinical symptoms of exercise induced laryngeal obstruction

EIIS is commonly mistaken for EIA and patients may have been treated for years without the correct diagnosis being considered (Rogers & Stell 1978). The main difference between EIIS and wheeze related to EIA is that EIIS develops when the requirement for ventilation is at its greatest. The breathing problem is usually evident during the inspiration phase of respiration and may end in hyperventilation or panic attacks. Symptoms of EIIS usually disappears 2-3 min after exercise ceases (Christopher 2006; Christopher & Morris 2010; Morris & Christopher 2010). Patients with EIA on the other hand, can manage well during exercise but get expiratory breathing difficulties and wheeze most often 3-15 min after exercise has stopped (Anderson et al. 1975).

EIIS is not a strictly defined symptom, but a relatively vague description of a compound series of symptoms that usually occur in sequence. EIIS is therefore open for individual and subjective interpretations, and may not be accurate. Symptoms like prolonged inspiration, shortness of breath and throat tightness represent the initial phase, while stridor, high-pitched inspiratory noise, hyperventilation and panic reactions tend to represent an end point forcing most patients to stop exercise. Whether symptoms are perceived as a problem by patients is influenced by how often and to what extent they exercise and by personal ambitions in relation to why they exercise. In other words, relatively similar symptoms may be interpreted differently by patients according to factors relating to personal ambitions and lifestyle.

In the present study, a standardized treadmill test for exercise induced asthma had been performed in most patients included. By doing so, two important means were accomplished. Firstly, EIA could be excluded as the cause of the presenting complaints. Secondly, the symptoms presented by the patients could be verified by our research group as being consistent with those of EIIS. This increased the fraction of patients in the examined population who were likely to suffer from central airway obstruction. Also, since laryngoscopy during exercise is a semi-invasive and relatively resource intensive examination, it is appropriate to reproduce and verify the symptoms of the patient before performing the CLE-test. Obviously, as suggested by Rundell et al., the best would be to copy the field situations in which patients experience their breathing problems (Rundell & Spiering 2003).

Exercise induced asthma (EIA) can be diagnosed by performing a standardized exercise test and measure the variation in lung function from before to after exercise. (Carlsen & Carlsen 2002). Tests utilizing different types of exercise have been standardised for this purpose, exemplified by the work of M. Silverman, S.D. Anderson and S. Godfrey in the early 1970`s (Anderson et al. 1971). In children, running has been demonstrated to provoke EIA better than cycling and free running better than running on a treadmill (Anderson et al. 1971). Furthermore, running for 6-8 minutes provokes a greater decrease in post-exercise FEV_1 than running for shorter or longer time periods (Godfrey et al. 1975). Patients with EIA exhibit quite characteristic changes of lung function when tested. During most of the active exercise period, the lung function changes little or may even improve. The fall in lung function normally occurs 3-15 minutes after stopping the exercise (Anderson et al. 1975) and values normally returns to baseline within 30-45 min (Godfrey & Bar-Yishay 1993; Silverman & Anderson 1972).

When using the EIA test to reproduce symptoms of EIIS, it is of particular importance that the respiratory pattern, the degree of dyspnoea, distress, hyperventilation attacks, panic reactions and respiratory sounds during the test are meticulously recorded.

5.6.2 Lung function tests in the diagnostics of EILO

Several studies have described abnormal inspiratory flow volume loops (FVL) in patients with EIIS while at rest (Christopher et al. 1983; Corren & Newman 1992; Kivity et al. 1986; Lakin et al. 1984; McFadden, Jr. & Zawadski 1996; Morris et al. 1999; Newman et al. 1995; Rundell & Spiering 2003). According to Christopher (Christopher & Morris 2010), the most common causes of a blunted or truncated inspiratory flow-volume curve are inadequate instruction, suboptimal effort or inability to perform the procedure. The sensitivity of the flow volume loops performed at rest has been reported to be low in relation to identifying patients with symptoms of EIIS (McFadden, Jr. & Zawadski 1996; Morris et al. 1999; Newman et al. 1995). McFadden et al. (McFadden, Jr. & Zawadski 1996) found pulmonary function tests (PFTs) to be normal at rest, variable when symptomatic, and normal within 1 min of symptom resolution in elite athletes diagnosed with VCD. Morris et al. found that inspiratory truncation did not distinguish between VCD positive and VCD negative patients (Morris et al. 1999). Rundell could not distinguish resting PFT measurements between subjects with inspiratory stridor and control subjects and could not find obvious inspiratory truncation (Rundell & Spiering 2003). Kenn suggested that VCD should be suspected when the ratio FEF_{50}/FIF_{50} exceeded one (Kenn & Balkissoon 2011). Christopher stated that during ongoing symptoms of VCD, all subjects demonstrated an elevated FEF_{50}/FIF_{50} ratio exceeding two (Christopher et al. 1983). Rundell found elevated FEF_{50}/FIF_{50} ratio > 1,5 during ongoing symptoms in 33% of subjects with stridor.

Most authors have concluded that metacholine challenge tests are of little value to distinguish between EILO and asthma since the two conditions often co-exist (Brugman & Simons 1998; Christopher & Morris 2010; McFadden, Jr. & Zawadski 1996; Rundell & Spiering 2003).

In conclusion, based on the literature at this stage, making a diagnosis of EILO on the basis of lung function tests seems tenuous. There is no consistent evidence in the literature to suggest that EILO can be diagnosed on the basis of baseline lung function tests.

5.6.3 Laryngoscopic evidence of EILO

Visualization of paradoxical adduction of laryngeal structures during exercise induced ongoing dyspnoea has been proposed the “gold standard” for diagnosing EILO (Beaty et al. 1999; Bent, III et al. 1996; Christopher & Morris 2010; Kenn & Balkissoon 2011; McFadden, Jr. & Zawadski 1996; Morris & Christopher 2010; Rundell & Spiering 2003; Tervonen et al. 2009; Wood & Milgrom 1996). Christopher and Morris presented data from a literature review of 355 articles on this issue. Laryngoscopy during symptoms was not performed in 38% of patients (Christopher & Morris 2010). Laryngoscopy was found to be diagnostic in only 60% of symptomatic patients (Newman et al. 1995). There are several possible reasons for this result. Importantly, symptoms resembling EIIS may be related to extra-laryngeal pathology in an unknown proportion of patients. Also, the test situation may be inadequate in terms of reproducing the symptoms in an unknown proportion of patients.

Morris and Christopher have described a procedure for flexible laryngoscopy in patients with POLO (Morris & Christopher 2010), and recommended the following evaluation: (1) The supraglottic and glottic anatomy, including supraglottic prolapse and occurrence of tumors or other lesions. (2) The appearance of the laryngeal mucosa and signs of inflammation. (3) The movements of the glottic structures, including the true vocal cords, false vocal cords, arytenoids, and surrounding structures. This diagnostic approach was based on post-exercise laryngoscopy.

Direct observation of the larynx as symptoms increase has been suggested by some authors (Bent, III et al. 1996; Weinberger & Abu-Hasan 2007). They argue that airflow obstruction in otherwise healthy individuals may be present only at high airflows. Since airflow as well as symptoms decrease rapidly after exercise (McArdle et al. 1995), laryngeal examinations before as well as after exercise is not likely to be informative.

There is no consensus in the literature regarding what is a pathological adduction of laryngeal structures during exercise. Greater than 50% inspiratory adduction of the vocal cords was suggested as diagnostic for exercise induced VCD by McFadden et al. in 1996 (McFadden, Jr. & Zawadski 1996; Morris et al. 1999). Regarding movements of other laryngeal structures, such as the aryepiglottic folds and the epiglottis, there are no data or no suggestions as to what is to be considered cut-off levels for normality.

5.7 Pathophysiological aspects of EILO

The literature on the pathogenesis of EILO is unclear, and dominated by mostly unsubstantiated speculations. The adduction of laryngeal structures observed during maximal exercise is likely to be related to high inspiratory airflows, and to changes in pressure gradients occurring across the larynx. Factors that may be involved are the cross-sectional area of the laryngeal aperture, the architecture and support from the laryngeal cartilage, fibrous tissue and muscles, the direction of the air flow through the larynx and down the trachea (e.g. turbulent vs. non turbulent flow) and laryngeal hyper-responsiveness. Psychological stress, in one form or another, has been implicated in these considerations by most authors (Dunglison 1842; Lacy & McManis 1994; McFadden, Jr. & Zawadski 1996; Patterson et al. 1974; Powell et al. 2000).

5.7.1 Laryngeal architecture and airflow resistance

Resistance to flow in the airways depends on whether the flow is laminar or turbulent and on the dimensions of the airway. With increasing metabolic demands during exercise, minute ventilation increases (Ferris et al. 1964). With higher flow rates, the laryngeal component of resistance increases more than that of the lower airways. The cause for this may be explained by the fact that approximately 90% of turbulent airflow seems to be located in the central airways (Ferris et al. 1964). As turbulent airflow generates more resistance than laminar airflow, resistance will increase proportionally more in the central airways than in the lower airways.

Increased airflow influences the pressure gradients over the laryngeal lumen. This phenomenon can be explained through the principles of aerodynamics, i.e. the principles of Bernoulli and Venturi and of Poiseuilles law. The relationship between the velocity and the pressure exerted by a moving gas is described by the Bernoulli`s principle: “as the velocity of gas increases, the pressure exerted by that gas decreases” (Fajdiga 2005). Translated into the environment of the larynx, this means that increasing airflow velocity leads to an increasing negative pressure inside the laryngeal lumen and therefore to an increasing inward pressure on the laryngeal architecture. Thus, as the level of exercise increases, so does the negative transmural pressure gradient that can eventually result in an inward collapse of laryngeal structures (Bjornsdottir et al. 2000; Mandell & Arjmand 2003). The larynx is protected from inspiratory collapse by a relatively rigid cartilage skeleton, particularly the cricoid cartilage, and muscular actions that provide support for the glottic- and supraglottic structures. Reidenbach suggests that a possible reason for the inward collapse that may be observed of the aryepiglottic folds may be insufficient anchorage of the cartilage skeleton of the larynx (Reidenbach 1998). A flaccid and/or oedematous and/or swollen and/or superfluous mucosa of the arytenoids and of the aryepiglottic folds may contribute by “disturbing” the airflow, thereby inducing a change from laminar to turbulent flow at an earlier stage. A retroflex or omega-shaped epiglottis may contribute in a similar way or by representing an obstruction by itself (Belmont & Grundfast 1984).

Abnormal airway noise like stridor or wheeze can be explained by the Venturi principle. With a linear movement of gas through a tube, lateral pressure decreases and creates a force acting towards a narrowing of the tube. The flexible part of larynx is subjected to these forces, which may suck these flexible or loose structures into the airway lumen. The narrowing of the lumen or the vibration of the lumen wall can result in audible sounds. The cross-sectional area of the larynx is important and potentially the most variable determinant with respect to the regulation of airway resistance. According to the law of Poiseuille`, a reduction of the radius of the laryngeal opening will increase the resistance to flow in the tube according to the fourth power of the radius. 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, produce sounds. The intensity of turbulence and the noise generated, increase with the rising flow velocity (Forgacs 1978).

5.7.2 Laryngeal hyperresponsiveness

The concept of a hyper-responsive larynx similar to the hyper-responsive airway in asthma, has been the focus of recent studies and has been proposed to explain the collapse of central airways in patients with EILO. Irritant associated EILO is hypothesized to represent an accentuation of the glottic closure reflex that may be released by various extrinsic or intrinsic stimuli that trigger laryngeal closure as a protective response (Balkissoon 2002). The larynx is highly innervated with sensory and motor nerve fibres, which are thought to become hyperexitable by exposure to various sorts of irritants. As a consequence, the hyperactive larynx should exhibit hyperfunctional glottic movements when exposed to certain triggers (Morrison et al. 1999; Yelken et al. 2009). Suggested intrinsic irritants include gastroeosophageal reflux disease (GERD), laryngopharyngeal reflux (LPR), post nasal drip (PND), chronic cough, laryngeal dryness, respiratory infections and exercise (Morrison et al. 1999). Suggested extrinsic factors include inhaled agents like medications, fumes or allergens (Bhalla et al. 2009).

Asthma has been associated with GERD in several studies. Closely associated with GERD is also laryngopharyngeal reflux (LPR), the retrograde movement of gastric contents into the laryngopharynx leading to symptoms of dysphonia, globus pharyngeus, dysphagia, cronic cough or nonproductive troat clearing (Belafsky et al. 2002; Bucca et al. 1995; Cukier-Blaj et al. 2008; Harding et al. 2000; Kenn & Balkissoon 2011). GERD may occur without the typical symptoms of heartburn. An association between VCD or laryngospasm and GERD has been reported from several studies (Goldberg & Kaplan 2000; Harding et al. 2000; Kenn & Balkissoon 2011; Koufman et al. 2002; Maschka et al. 1997; Morrison et al. 1999; Perkins & Morris 2002; Tilles 2003). Arytenoid and interarytenoid oedema with findings typically seen in GERD, have been described in patients with VCD, and causal relations have therefore been suggested. However, in many of these studies, esophageal pH monitoring was not performed, and treatment outcome after institution of proton pump inhibitors (PPI) was not reported (Powell et al. 2000). In a study by Morrison, twenty-five of 39 patients with “irritable larynx syndrome” were noted to have laryngospasm and as many as 92% of patients diagnosed to have GERD. Proton-pump inhibitors (PPIs) were routinely used for treatment, but symptomatic improvement was not reported (Morrison et al. 1999). In a recent study by Maturo et al., no effect of PPI was observed on exercise induced paradoxical vocal fold movement in patients with verified GERD (Maturo et al. 2011).

In summery, despite the many hypotheses, there is little prospective evidence defining the role of laryngeal hyperresponsiveness leading to VCD (Christopher & Morris 2010). It is important in this context to be aware that the prevalence of GERD in the general population has been reported to be as high as 10-60%, based on meta-analysis of studies using pH probes (Merati et al. 2005). It is also reported that GERD is present in 60% of patients with asthma (Field et al. 1996; Harding et al. 2000; Vincent et al. 1997). Given these high figures, putative causal associations with other diseases will require controlled studies.

5.7.3 Psychological stress related to EILO

The initial description of VCD by Christopher et al. emphasized underlying psychological disorders. Functional disorders, including depression, factitious disorders, conversion disorders and somatoform disorders have also been associated with VCD. Emotional stress is a well described precipitant of psychogenic VCD and may also play a role in EILO. Stressors including combat and competitive sport are noted as a trigger of VCD (McFadden, Jr. & Zawadski 1996; Morris & Christopher

2010; Powell et al. 2000; Rundell & Spiering 2003). The organic substrate through which psychological stressors should exert its effect has not been objectively defined in studies. One may speculate that stress somehow should lead to adductional signalling to laryngeal muscles, thereby reducing the lumen and inducing symptoms. However, these issues have not been addressed in studies utilizing objective test methods.

5.8 Treatment of patients with EILO

Treatment of EILO has so far been based on relatively weak evidence, and is also not the main focus of this thesis. To our knowledge, no randomized controlled trials utilizing objective outcome measures have been performed. Thus, Level I evidence does not exist for any of the suggested treatment options (Harbour & Miller 2001). Most authors have stressed that the management of EILO should include the exclusion of extra-laryngeal pathology causing respiratory distress during exercise. Historically, most of the various approaches to the management of EILO have been based on the paradigm that VCD or PVFM constitute the mechanisms that are responsible for the airflow obstruction. It seems that embedded in this paradigm, a strong focus on psychology and psychiatry has been important, and that various forms of stress mechanisms have been held responsible for the development of the malfunction of the organ. Naturally, this view has also influenced the strategies that have been applied for treatment. Thus, post-traumatic stress disorders or other types of psychological or psychiatric disorders have been described in relation to EILO in several reports (Brugman 2009; Christopher & Morris 2010; Morris & Christopher 2010; Rhodes 2008). In addition, overly focus on high performance in athletes may trigger or aggravate symptoms of EILO. Therefore supportive counselling has been focused in most publications on treatment, and referral to a psychiatrist or psychologist has been suggested in cases where conversion or panic disorders have been suspected. Treatment suggestions that have been put forward include psychotherapy, speech therapy, relaxation therapy, hypnosis and biofeedback

(Andrianopoulos et al. 2000; Kayani & Shannon 1998; Maillard et al. 2000; McQuaid et al. 1997; Murry et al. 2004; Sullivan et al. 2001).

Speech therapy has been reported to be the mainstay of treatment in VCD patients (Andrianopoulos et al. 2000; Christopher & Morris 2010; Kayani & Shannon 1998; Lakin et al. 1984; Landwehr et al. 1996; Maturo et al. 2011; McFadden, Jr. & Zawadski 1996; Morris et al. 1999; Newsham et al. 2002; Sullivan et al. 2001). Although speech therapy focusing on respiratory control and diaphragmatic breathing patterns has been reported to be successful, the treatment programs have not been specifically described in the articles and there have been limited follow-up studies with specific outcome data reported. Additionally, few studies have applied and assessed speech therapy as their only treatment approach, further complicating interpretation.

Weinberger reported that an anticholinergic aerosol (ipratropiumbromide) applied before exercise could prevent what he called exercise induced paradoxical vocal cord adduction (Weinberger & Abu-Hasan 2007). Pharmacological agents have otherwise been used to decrease the impact from triggers of paradoxical vocal cord motion (Wilson & Wilson 2006).

Inspiratory muscle strenght training (IMST) has been reported effective in case reports (Baker et al. 2003; Mathers-Schmidt & Brilla 2005; Ruddy et al. 2004; Van et al. 1983). The theory is that the diaphragm and the posterior cricoarytenoid muscle (the main abductor of the larynx) are closely related, and that inspiratory muscle training activates both, opening for a more effective laryngeal abduction.

Different biofeedback techniques have also been suggested by some to be beneficial (Earles et al. 2003; Rhodes 2008).

For supraglottic EILO, some authors have proposed a surgical procedure similar to the technique used for congenital laryngomalacia, i.e. laser supraglottoplasty (Bent, III et al. 1996; Maat et al. 2007; Mandell & Arjmand 2003; McClurg & Evans 1994; Smith et al. 1995). Smith demonstrated that removal of the corniculate cartilages using laser in patients with a supraglottic collapse of tissue during exercise was associated with improvement of endurance and physical fitness (Smith et al. 1995).

Positive effects from supraglottoplasty or epiglottopexy have been demonstrated in selected cases with the supraglottic EILO (Maat et al. 2007; Mandell & Arjmand 2003; Nonomura et al. 1996; Siou et al. 2002; Whymark et al. 2006).

6. Aims of present studies

I To develop a test method for visualization, objective measurements and documentation of laryngeal function during ongoing heavy treadmill exercise. It should be possible to combine this test with a complete cardiopulmonary exercise set-up. Its feasibility and tolerability should be demonstrated in subjects of the relevant age group, i.e. children and young adults, with and without symptoms resembling exercise induced inspiratory stridor (EIIS).

II To use this test, called Continuous Laryngoscopy Exercise-test (CLE-test), in an observational study design, in order to explore laryngeal response pattern(s) to exercise in a large group of children and young adults with symptoms of EIIS and in control subjects with no such symptoms.

III To use the CLE-test to grade and characterize (supraglottic or glottic or otherwise) exercise induced laryngeal obstruction (EILO), and to investigate its development during increased ventilatory requirements throughout a maximal exercise test.

IV To develop a score system based on findings from the CLE-test. Intraobserver and interobserver repeatability and the validity of the scoring system should be assessed in a mixed population of subjects with and without symptoms of EIIS.

7. Study design, subjects and methodology

7.1 Study design

The present thesis reports results from a descriptive cross-sectional observational clinical study of patients with exercise induced inspiratory shortness of breath. The laryngeal response to physical activity in subjects without symptoms is poorly described in the literature. Therefore, 20 volunteers without self-reported shortness of breath during exercise were invited to participate as control subjects.

7.2 Ethics

The Regional Ethics Committee approved the study and informed written consent was obtained from all participating subjects or their guardians. The study met the criteria listed by Emanuel et al. in their paper "What Makes Clinical Research Ethical" (Emanuel et al. 2004) and was also approved by Norwegian Social Science data Services (NSD).

7.3 Subjects

Paper # 1. Twelve healthy medical students and four female athletes exhibiting EIIS during high intensity treadmill exercise were recruited as control subjects and patients (cases), respectively. The study served as a pilot study to test the feasibility of the CLE-test and to evaluate normal and potentially abnormal laryngeal motion during exercise.

Paper # 2. Patients (n=166) were consecutively recruited over a period of six years (2002-2007) from the outpatient pulmonology clinic at the Paediatric Department, Haukeland University Hospital, Bergen, Norway. The CLE-test was performed in patients with a history of exercise induced dyspnoea, symptoms of EIIS and no evidence of EIA on a standard exercise provocation test (Carlsen et al. 2000). EIIS was defined by a prolonged inspirium, inspiratory distress, stridor, chest pain, hyperventilation attacks or frank panic reactions occurring during exercise (Christopher et al. 1983; Heimdal et al. 2006; Rundell & Spiering 2003). The control group included 20 volunteers, with approximately the same distribution of gender as in the patient group, however slightly older.

Paper # 3. Patients and controls were recruited from the same groups as contributing in paper # 2. Provided that some degree of respiratory distress had been observed during the CLE-test, and that the video recordings were of adequate quality, 80 patients were selected for assessment of intra- and inter-observer repeatability, and of the validity of the findings in relation to symptom scores. The same 20 volunteers as in paper # 2 served as symptom negative control subjects.

Paper # 4. Three patients with unilateral vocal cord paralysis were observed among patients with EIIS included in paper # 2. One of these patients was a survivor of extreme preterm birth, participating in a long-term follow-up study that was running in our laboratory in parallel to the present study, focusing on young adults born in western Norway in 1982-85 with gestational age ≤ 28 weeks or birth weight ≤ 1000 grams (Halvorsen et al. 2004). This patient had a left sided vocal cord paralysis (LVCP) and a neonatal history of surgical treatment of a patent ductus arteriosus (PDA). This finding lead to a search in the complete cohort of 46 subjects of the parallel study of ex-preterm adults. In the neonatal period, 33 (65%) of them had been diagnosed with a clinically significant PDA and 13 (26%) had been surgically treated. Seven (54%) of these subjects had LVCP on laryngoscopy and they were all subsequently offered a CLE- test.

7.4 Diagnostic tests

No subjects were examined within two weeks of a respiratory tract infection. The room temperature of the laboratory was 20-25 ˚C and humidity was less than 50% (Sterk et al. 1993). Calibration of the equipment was performed prior to each test in accordance with the instructions given in the manufacturers manuals (SensorMedics & The Cardiopulmonary Care Company 1995). A general physical examination by a physician was performed prior to diagnostic tests.

7.4.1 Spirometry

Lung function was measured by maximal forced expiratory flow volume curves (SensorMedics Vmax 29, Yorba Linda, CA, USA), applying quality criteria according to the guidelines of the European Respiratory Society (Quanjer et al. 1993), and values were reported as percentages of predicted (Knudson et al. 1983; Quanjer et al. 1993; Sterk et al. 1993).

7.4.2 Exercise Induced Asthma test (EIA-test)

EIA tests were performed by letting subjects run on a motor-driven treadmill for 8 minutes with a submaximal exercise load. The inclination on of the treadmill was 5.5%. The treadmill speed was adjusted individually in order to achieve a steady state heart rate of at least 85% of calculated maximum heart rate (220 – age) for the last 4 min of the running time. The heart rate was monitored electronically by a Sport tester (Polar Accuex Plus, Finland). FEV_1 was measured before running, immediately after, and 3, 6, 10 and 15 min after stopping of exercise. Symptoms of noisy breathing, prolonged inspirium, inspiratory distress, stridor, chest pain, hyperventilation attacks or panic reactions occurring during exercise were observed and recorded.

7.4.3 Continous Laryngoscopy Exercise test (CLE-test)

An integrated set-up was developed, combining equipment for laryngoscopy, video and sound recording with an ergo-spirometry unit (Fig 4 s. 45). The experimental set-up was tested in a group of adult volunteers and technically adjusted according to comments. A specially developed head set and a facemask (Hans Rudolph inc., Wyandotte, USA) served to secure the laryngoscope to the head of the test subject and to prevent movements of the camera while the test subject was running. The ergospirometry unit was connected with the facemask through sample lines and the flow sensor. The face and the upper part of the body were video-recorded using an external video camera in order to document the movements of the test subject and signs of respiratory distress. Respiratory sounds were recorded with a microphone placed in front of the head of the test subject, close to the facemask. A computerized protocol for ergo-spirometry was used in all test subjects. During the test, exercise flow volume loops (extFVL) were recorded at pre-planned and regular intervals while measures of gas exchange (Vmax29, Sensor Medics), and a 12 lead ECG (Marquette Medical Systems inc., Milwaukee, USA) were continuously recorded.

Test performance.

An adrenergic agonist was applied in the nostrils 10 minutes before anaesthetizing the nasal cavity with lidocaine. The head set and the facemask were adjusted to the patients head. A flexible fiberoptic laryngoscope with diameter 3.6 millimetres and length 255 millimetres (Olympus ENF-P3, Tokyo, Japan), was advanced through an open silicon plug in the facemask and then advanced further through the nasal cavity and into the oropharynx. When in correct position, the laryngoscope was secured to the head set. An endoscopic video camera system (Telecam, Karl Storz, Tuttlingen, Germany) was connected to the fiberoptic laryngoscope. The external video camera and the microphone were placed in front of the test subject, and finally the ergo-spirometry unit was attached to the facemask by means of the appropriate sample lines. The parameters of gas exchange were recorded using “breath by breath” method. Test subjects were running on a treadmill, Ergo ELG70 (Woodway, Weil am Rhein, Germany) to individual experience of exhaustion. We used an incremental test set-up, based on a modified Bruce protocol (Cumming et al. 1978), aiming to obtain PeakVO_2 after 6-12 minutes of exercise.

The following variables of gas exchange were recorded: Minute ventilation (MVE), tidal volumes, peakVO_2, respiratory quotient (RQ) and tidal exercise flow volume loops (extFVLs). Tidal exercise flow volume loops were recorded approximately every second minute. The test was terminated when test subjects were exhausted or experienced symptoms of stridor preventing further running. The maximal work capacity was determined by measuring peakVO_2. The ventilatory reserve (VR) at exhaustion was determined by subtracting measured MVE from the calculated maximal minute ventilation (MMV=FEV_1 x 35) (Johnson et al. 1999). Tidal exercise flow volume loops were plotted within the baseline maximal flow volume loop (MFVL). The end-inspiratory lung volume (EILV) and end-expiratory lung volume (EELV) within MFVL may be graphically illustrated (Johnson et al. 1999).

The test was considered successful if the patient reproduced his or her respiratory complaints, or indicated exhaustion, preferably supported by a plateau in oxygen consumption and/or the heart rate response.

7.4.4 CLE-test scoring system

The video recordings were reviewed and scored throughout the exercise session according to a preset protocol. The position and movements of the glottic (vocal cords) and supraglottic (the cuneiform tubercles and aryepiglottic folds) structures were scored. If laryngeal adduction occurred, the sequence of events was determined, i.e. if adduction started in supraglottic or in glottic structures. The timing of the onset of symptoms (EIIS) and of the onset of laryngeal adduction was determined. Whenever possible, epiglottic movement was determined as normal or retroflex.

The results were compared in a blinded fashion with respiratory noise and external video recordings of the upper part of the body (neck and jugulum). Clinical symptoms and the tolerability of the CLE-test were recorded in a questionnaire. All scores were done in retrospect by using the video-recordings with the observer blinded to the status of the test subject in terms of being a patient or a symptom negative control.

7.4.5 PDA ligation.

The surgery for PDA had been performed during the neonatal period of the preterm participants reported on in paper # 4, i.e. at average 18 years before inclusion to the present study. Surgery had been performed between the 4th and 29th day (mean 12) in infants failing to wean from mechanical ventilation after echocardiography had confirmed presence of a haemodynamicly significant PDA. The chest had been accessed through an anterolateral thoracotomy, whereupon the ductus arteriosus had been dissected free from surrounding tissue and closed with a metal clip. Four different cardiothoracic surgeons had performed the operations according to identical procedures (Mandhan et al. 2006; Spanos et al. 2009). A written report was available at inclusion to the present study in 12 of the 13 patients. The left recurrent laryngeal nerve was commented on in five patents, and positively avoided in three.

7.4.6 High resolution CT scanning (HRCT) of the lungs.

Examinations had been performed in 2001 in conjunction with the first assessment of the preterm participants reported on in paper # 4. Methods and overall results have been described elsewhere (Aukland et al. 2009). Findings typical for aspiration were searched for particularly in subjects with LVCP (de Benedictis et al. 2009).

7.4.7 Questionnaire

In addition to an interview, a standardized questionnaire served to obtain the medical history, information of symptoms in relation to exercise, the activity level of the test subject and the influence of EIIS on daily life activities. A visual analogue scale (VAS) served to grade the severity of symptoms and respiratory complaints during exercise.

7.5 Statistical analyses

Paper # 1 and # 2. Only group mean values and standard deviations are reported.

Paper # 3. Agreement between and within the observers (sum of scores and sub-scores) was examined with Κ statistics. Κ values were interpreted according to Altman (ref); i.e. Κ: < 0,20 = poor, Κ. 0,21- 0,40 = fair, Κ: 0,41- 0,60 = moderate, Κ: 0, 61- 0,80 = good and Κ: 0,81-1,00 = very good agreement. Weights were given to disagreement according to the magnitude of the discrepancy. The numbers of paired observations with exact inter- and intra-observer agreement were calculated.

Correlations between laryngeal scores and the scores for respiratory distress were assessed with Spearman's *p*-test (Altman 1995). The concordance between sub-scores and the sum score was analyzed by Cronbach's α-test. Chi- square tests were used to assess whether sum scores from patients and symptom–negative controls differed. The ability of observers to separate patients and controls by the use of sum scores was also evaluated by variance analyses. Differences between patients and controls with regard to each sub-score were further evaluated by variance and regression analyses. The calculations were made with the statistical program package SPSS (Ver. 15; SPSS inc., Chicago, Il, USA). All reported *P*- values are two tailed, and $P <$ 0,05 was considered statistical significant.

Paper # 4. Chi square tests, Student's t-tests or one way analyses of variance (ANOVA) were used for group comparisons of categorical and numerical data, as appropriate. As the size of the groups and the distribution of the variables could not be known in advance, a priori power calculation was not possible. We report most data as mean values with 95% confidence intervals without p-values.

8. Results and synopsis of papers

8.1 Paper # 1

This paper presents the method which constitutes the basis for this thesis.

Larynx accounts for a significant fraction of total airway resistance, but its role as a limiting factor for airflow has been hampered by lack of diagnostic tools. The purpose of this study was to describe a new method for examination of larynx during exercise in patients with exercise induced inspiratory stridor. A complete cardiopulmonary exercise test was combined with flexible transnasal fiberoptic laryngoscopy in patients running on a treadmill (Figure 4). The tolerability and the diagnostic success rate of the method were studied.

Figure 4.

Illustration: Gørill Skaale Johansen

The study concludes that continuous laryngoscopy during incremental maximum treadmill exercise is possible, feasible, and well tolerated in young adults. The study served as a pilot, indicating that healthy young subjects without respiratory complaints could be separated from patients complaining of symptoms of EIIS.

8.2 Paper # 2

This paper presents the main results from the work that constitutes this thesis.

The aim was to investigate the laryngeal response patterns to exercise in a large group of patients complaining of EIIS. The CLE-test was applied in 166 subjects recruited over a period of six years, basically from the out patient clinic at the Pediatric Department at Haukeland University Hospital. The set-up facilitated visual access to the larynx from commencement of symptoms to the patient was stopped from further exercise, either by exhaustion or due to symptoms of EIIS. This had never been attempted in any previous study, prior to this. Twenty volunteers without self-reported shortness of breath during exercise were invited to participate as control subjects, with the purpose to address normal laryngeal response(s) to exercise.

Table 1

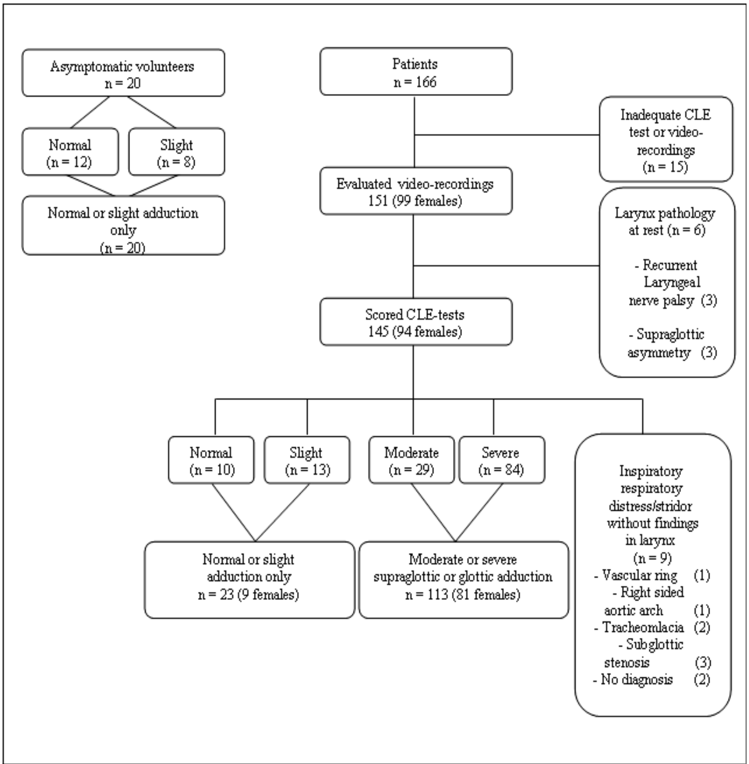


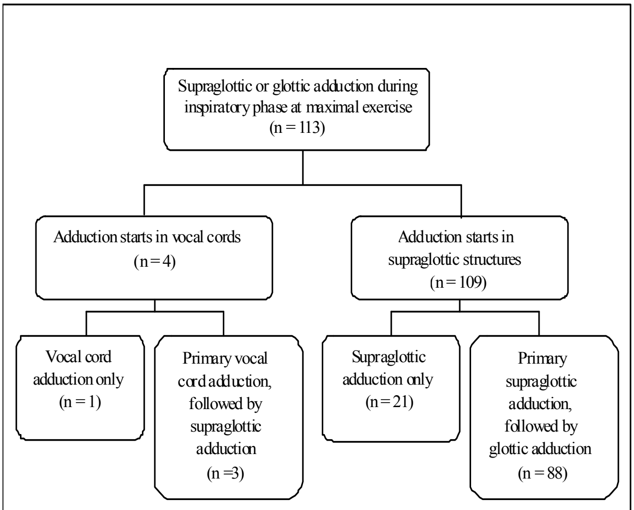
Diagram showing the main findings of the study. Normal, slight, moderate and severe refer to the worst extent of laryngeal adduction observed during the exercise test, supraglottic or glottic irrespective

Treatment of asthma during the year preceding the CLE-test was reported by two (10%) of the controls, and by 128 (85%) of the patients, 82 (64%) of whom reported no effect on exercise related symptoms.

Successful CLE-tests with video recordings of acceptable quality were obtained in all 20 control subjects and in 151 (91%) patients (Table 1). A mild medial rotation of the cuneiform tubercles was observed at maximum exercise in eight (40%) controls. For the purpose of this study, therefore, a mild adduction of supraglottic structures at maximum intensity exercise was classified as a negative response.

Based on this cut-off value, CLE-tests diagnostic of EILO was observed in 113 (75%) of 151 patients. The most typical response pattern was characterised by a normal laryngoscopy at rest and moderate or severe adduction of laryngeal structures during heavy exercise. In 109 (97%) of these 113 patients, the laryngeal adduction started as medial motion of the aryepiglottic folds and/or the cuneiform tubercles (Table 2).

Table 2.



Sequence of events with respect to laryngeal adduction in patients with exercise induced laryngeal dysfunction.

Eighty-eight (81%) of these 109 patients had a secondary medial motion of the vocal cords. In four (3%) of the 113 patients, adduction was initiated by a medial motion of vocal cords, followed by a secondary supraglottic adduction in three of them. Hence, a combined supraglottic/glottic adduction was observed in 91 (81%) of the 113 patients.

Six patients (4%) had an asymmetrical larynx at rest, diagnosed as vocal cord paralysis (n=3) or supraglottic asymmetry (n=3). This indicates that laryngoscopy at rest has little diagnostic value in relation to EILO. Four of these patients had audible inspiratory stridor and two had a prolonged and abnormal inspirium during the CLE-test. All had an increasing asymmetrical medial motion of supraglottic structures paralleled with increasing symptoms throughout the exercise session. Findings were particularly pronounced in the patients with a unilateral paralysis of a vocal cord, with the ipsilateral aryepiglottic fold reaching or even crossing the midline and thereby almost closing the laryngeal entrance.

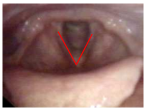
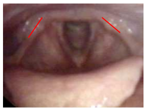
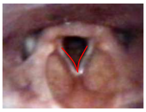
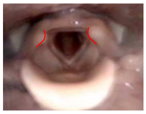
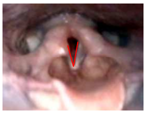
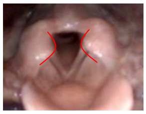
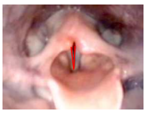
Four patients (3%) had supraglottic findings at rest that resembled laryngomalacia, i.e. an omega shaped epiglottis, enlarged aryepiglottic folds and a narrow laryngeal entrance. All of them had a dysfunctional supraglottic laryngeal exercise response with stridor already at moderate intensity. None of these four patients had a history of breathing problems in early childhood suggestive of pediatric laryngomalacia.

Nine patients (6%) had a normal laryngeal exercise response but a clearly abnormal respiratory pattern, closely resembling EIIS during high intensity exercise. Thus, in these patients the CLE-test was positive in terms of audible findings and respiratory distress, but negative in terms of laryngeal findings. Structural obstructions of central airways were diagnosed in seven of these patients, caused by vascular compression, tracheomalacia and subglottic stenosis. These patients had not been correctly diagnosed if not referred for further investigations after the CLE-test. Clinically, in our view, their symptoms could not be distinguished from other patients with EIIS.

Typical high-pitched inspiratory stridor was recorded in 90 (60%) of the 151 patients enrolled, and in 77 (68%) of the 113 patients with a moderate or severe adduction of laryngeal structures during exercise. A coarse or noisy inspirium were the most common audible symptoms in the remaining patients. The 23 patients with only mild or no laryngeal obstruction had milder clinical symptoms, such as heavy breathing and prolonged inspirium.

8.3 Paper # 3

This paper presents an assessment of the validity of laryngeal findings in relation to symptom severity and of the repeatability of the observations.

Figure 5	***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. With permition Eur Arch Othorhinolaryngol.

The proportion of inter-observer and intra-observer agreement for each sub-score varied between 70 and 100% (weighted κ values varied from 0.49 to 1.00, correspondingly). A positive correlation was found between CLE-test sum score (Figure 5) and symptom score (p = 0.75, P < 0.001). There was a significant difference in CLE-test sum score between patients (3.34; SD ± 1.34) and the volunteers without symptoms (0.65; SD ± 0.66) (P < 0.001). Thus, the study suggests that the presented scoring system is reliable and valid, and that it can be used when laryngeal function during exercise is evaluated.

8.4 Paper # 4

This paper presents a subgroup of patients with EIIS and EILO.

Left-sided vocal cord paralysis (LVCP) is a recognized neonatal complication from treatment of patent ductus arteriosus (PDA) in extremely preterm (EP) born infants. However, incidence rates and consequences for later life are poorly described. Follow-up studies after early childhood do not exist. The present study utilized the CLE-test to investigate long-term respiratory consequences from LVCP after neonatal surgical treatment of PDA.

The subjects participating in this paper are described in detail in the methods section, chapter 6.3. They were recruited from a parallel study running in the Pediatric Cardiopulmonary Test Laboratory, examining a population-based cohort of adults who were born at gestational age ≤ 28 weeks or with birth weight ≤ 1000g in western Norway in 1982-85 (Halvorsen et al. 2004). The incidental findings of LVCP in patients with EIIS incited an offer of laryngoscopy and a CLE-test to all EP born participants of the parallel study, providing they had a neonatal history of surgical treatment of PDA.

The study indicates that LVCP may be observed in approximately 50% of subjects who are born extremely preterm and treated operatively for PDA in their neonatal period. The observed prevalence rates are in line with studies of comparable infants, born at very low or extremely low birth weight (Clement et al. 2008; Smith et al. 2009). The results indicate that LVCP acquired in infancy cause symptoms in adulthood. All but one subject had voice related complaints and were regarded as hoarse by their family. All subjects were uncomfortable with singing and talking out loudly. One subject had a history of severe and recurrent “attacks” in infancy for which he had been hospitalized on several occasions. Three subjects had a history of “difficult-to-treat-asthma”. All three reduced their asthma medication substantially after being diagnosed with LVCP with no reported increase of symptoms. A fourth subject developed cyanosis when exercise tested, attributed initially to severe bronchopulmonary dysplasia and chronic airway obstruction, which she also had. Her LVCP was correctly diagnosed in the present study.

When tested with the CLE-test, an increasing anteromedial rotation of the left cuneiform tubercle and the left aryepiglottic fold was observed in all subjects as the exercise session proceeded. At maximum exercise, the left supraglottic structures severely compromised the laryngeal entrance. As viewed through the laryngoscope, the airflow had to follow an increasingly twisted pathway through the larynx to enter the lower airways. The presence of LVCP explained most of the airway obstruction observed with BPD in this cohort.

The study concludes that LVCP after surgical closure of PDA in extreme preterms may easily be overlooked and symptoms confused with those of other diseases. Laryngoscopy should therefore be offered on liberal indications after PDA ligation, and a CLE-test will aid the diagnostic considerations and possibly the treatment strategy for the individual patients. LVCP may be involved in the development of airway obstruction in extremely preterm born patients with BPD.

9. Discussion

The present thesis demonstrates that continuous laryngoscopy throughout a complete incremental maximum exercise test on a treadmill is possible, feasible and well tolerated. Exercise induced laryngeal pathology could be video-recorded and the findings correlated well with exercise induced symptoms as reported by the patients and as observed in the test situation. We were unable to link symptoms of EIIS to one single causal factor. This heterogeneity of findings in patients with relatively similar symptoms calls for caution with respect to classification or labelling of patients based on symptoms alone.

The CLE-test provides a tool for continuous review of the changing dynamics of laryngeal structures in each phase of the respiratory cycle as the exercise load increases, concurrent to objective measurements of variables of gas exchange. The test can relatively easy be implemented in a laboratory-setting for ergospirometry and may therefore serve as an important tool in the diagnostic work-up of patients complaining of respiratory symptoms during exercise. Parameters of ergo-spirometry and exercise tidal flow volume curves can be achieved and included in an extensive assessment of the exercise capacity of the patient. These data were not fully explored within the frames of the present thesis.

As symptoms of EIIS typically occur during vigorous exercise and usually resolves spontaneously within few minutes after its termination, direct observation of the larynx from the beginning to the end of symptoms seems important. The CLE-test provides an opportunity to review the progress of laryngeal dysfunction during a complete exercise session, from rest to exhaustion. Video recordings facilitate retrospective reviews of findings in a blinded fashion and also comparisons of results obtained from multiple tests of the same patients or between patients. The CLE-score system seemed valid, reliable and robust. Numerical scores facilitate comparisons between studies of different groups and between studies performed by different researchers in different populations, and permit the use of a variety of statistical analyzes.

This discussion will focus on methodological aspects of the CLE-test and its applicability in terms of clarifying the importance and the relevance of pathology and dysfunction of the central airway in patients complaining of EIIS.

9.1 Subjects.

9.1.1 Patients

A major strength of this study was the large population of patients included. This is by far the largest study described in the literature to date where laryngoscopy is performed during exercise. The patients were unselected, since Haukeland University Hospital is the only centre in the area for adolescents with this sort of medical problem. The CLE-test was performed in patients with observed exercise induced inspiratory distress or stridor, or a clearly abnormal breathing pattern with no evidence of EIA during a standard exercise provocation test (Carlsen et al. 2000). Asthma medication had been prescribed to most patients, but without effect in the majority (Table 1 paper # 2). Since the patients in the study were recruited mainly from the outpatient pulmonology clinic at the Pediatric Department and most had a medical history of asthma or suspected EIA, one can not exclude a sample bias. Unless laryngeal hyperresponsiveness constitute the explanatory framework for EIIS, thereby linking asthma and laryngeal dysfunction (Landwehr et al. 1996; McFadden, Jr. & Zawadski 1996; Newman et al. 1995; Rundell & Spiering 2003; Wilson & Wilson 2006), we can see no clear reason why asthma and EILO should be connected. This issue has also no clear answer in the literature; however, several theories have emerged from small clinical studies (Benninger et al. 2011).

Of the 13 subjects included in paper # 4, laryngoscopy was performed in 11 (85%). One of the remaining two subjects did not accept the procedure, while one did not wish to participate in the study. Left vocal cord paralysis was demonstrated in seven subjects. The CLE-test could not be performed in four of these subjects. In two of these subjects it was considered unethical to ask due to co-morbidities while two subjects declined.

9.1.2 Control subjects.

Twenty volunteers with no history of symptoms resembling EIIS were recruited to demonstrate a normal laryngeal response-pattern to exercise. These control subjects matched the patient group with regard to distribution of gender (patients: 66% females versus control subjects: 65% females). It was a weakness of the study that the control subjects were slightly older (patients: mean age 16.3 years versus control subjects: 22.7 years), and also substantially fewer than the patients. Since the procedure was expected to be somewhat uncomfortable, a higher number of younger control subjects were not examined for ethical reasons. The larynx may be changing during puberty, and this factor may be related to the extent by which young people are susceptible of experiencing EIIS. Ideally, therefore, age matched control subjects should have been recruited. Also, only 20 control subjects are too few to establish solid knowledge on what sort of normal variability is to be expected regarding the laryngeal response pattern to exercise. Thus, solid data for cut-off levels regarding the disease or the syndrome of EILO are yet to be established. Nevertheless, the twenty asymptomatic subjects examined in the present study constitute the largest series published to date on normal laryngeal response patterns to exercise.

9.2 Diagnostics of exercise induced laryngeal obstruction

Patients do not approach the doctor expressing that he/she suffers from shortness of breath during exercise related specifically to the throat or to the lungs. Usually, patients simply complain of shortness of breath during exercise, and it becomes the challenge of the doctor to figure out why. A good medical history or a good questionnaire to identify symptoms may be helpful. Ideally, symptoms should unequivocally identify the disease or objective tests should be available that could differentiate between the diseased and the healthy and between various disease conditions. Only then can a definite diagnosis be made. This, however, requires that definite limits have been defined that can identify those who are diseased.

9.2.1 Clinical symptoms of EIIS

This study suggests that EIIS in young patients is frequently confused with EIA. Treatment of asthma during the year preceding the CLE-test was reported by two (10%) of the control subjects and by 128 (85%) of the 166 patients with EIIS. Eighty-two (64%) of the patients reported no effect from asthma medication with respect to exercise related symptoms (Table 1 paper # 2).

The clinical history and the symptoms presented by the patients may not be properly utilized for diagnostic purposes. When reviewing the symptoms presented by the patients participating in the present study, clues to a diagnosis of upper airway obstruction were present in a large proportion. A good medical history or a good questionnaire designed to distinguish between symptoms of asthma and EILO probably has a good pre-selection value. Thus, as reported in paper # 2, the fraction of patients with positive findings during the CLE-test was relatively high. It is reasonable to assume that this was partly related to the selection of patients for testing.

Symptoms of EIIS are described to peak towards the end of an exercise session and during the first 2-3 minutes of recovery (Christopher 2006; Christopher & Morris 2010; Morris & Christopher 2010), whereas symptoms of EIA typically peaks 3-15 min after exercise has stopped (Anderson et al. 1975). These descriptions fit well with the experiences of the present study. When questioned if their breathing difficulties were worst during inspiration or expiration, most patients were unable to answer. However, if asked to rethink this issue during a week or so, most were able to respond. Furthermore, a question of the duration of symptoms after stopping the exercise may increase the diagnostic sensitivity of the medical history. Symptoms that tend to settle within the first few minutes after stopping the exercise are susceptible of EIIS.

In a study by Tervonen et al. (Tervonen et al. 2009) of 30 patients with suspected exercise induced VCD, only 15 patients could reproduce their dyspnoea when tested, and laryngoscopic findings of exercise induced VCD could be demonstrated in only nine (30%) subjects. This study primarily demonstrates the importance of reproducing symptoms when laryngoscopy is performed for diagnostic purposes in relation to EILO in patients with EIIS; i.e. the test set-up must ensure that the patients are comfortable and feel that they safely can perform at their maximal level.

Validation of the relation between central airway obstructions versus the compound constellation of symptoms that represent EIIS was beyond the scope of this thesis. However, the clinical experience gained by working with these patients indicates that there are certain aspects of the clinical history that with reasonable sensitivity and specificity seems to point to obstruction of the upper airways. The timing of symptoms in relation to the exercise session and within the respiratory cycle are central in this context.

9.2.2 Lung function testing in relation to EIIS

Spirometric findings may objectively define EIA, but there is no consensus regarding the role of spiromtry in relation to larynx dysfunction. Studies have reported variable and partly conflicting data (Christopher & Morris 2010; McFadden, Jr. & Zawadski 1996; Morris et al. 1999; Newman et al. 1995; Rundell & Spiering 2003). As stated in paper # 2, we were unable to identify typical patterns in baseline lung function performed at rest in patients with EILO. In some patients the shape of the flow volume loops (FVL) seemed abnormal, but not as expected with obstructive airway disease. Particularly, truncated or flattened inspiratory loops or expiratory loops shaped like a shoulder have been suggested as typical for EILO or central airway obstruction. Unfortunately, these curves are in our experience not diagnostic, since they may be observed also in patients without EIIS. These findings fit a recent retrospective review on this issue where only 36% of patients with these kinds of FVL shapes had VCD (Sterner et al. 2009).

Taken together, there is no evidence from the previous literature or from the present study to suggest that EILO can be diagnosed on the basis of baseline lung function tests.

9.2.3 Endoscopic examination in relation to EIIS

Direct observation of the larynx as symptoms evolve provides an opportunity to appreciate how laryngeal obstruction progress during the exercise session. Such knowledge seems important in order to establish a correct diagnosis, to clarify causal mechanisms and to develop evidence-based approaches to therapy. This line of reasoning was recently advocated also in a review on this issue (Weinberger & Abu-Hasan 2007). Most researchers of this area now seem to agree that endoscopic examination during symptoms is the best method to confirm the presence or absence and the characteristics of the laryngeal obstruction, and that this represents the "diagnostic gold standard" (Beaty et al. 1999; Christopher et al. 1983; McFadden, Jr. & Zawadski 1996; Morris et al. 1999).

One may question the use of the metaphor "gold standard" in this context. Laryngoscopy indeed shows what takes place in the larynx, but does not explain the functional correlates of the observations. One major challenge is the lack of consensus regarding what are the expected normal laryngeal response pattern(s) to exercise. Furthermore, there is a lack of knowledge on what is the required size of the laryngeal opening to allow free and unobstructed airflow during exercise. Given the large diversity between people regarding physical fitness and the corresponding and necessary diversity regarding the required maximum laryngeal airflow, there is obviously not only one answer to this question. What is an adequate size for a sedentary person, may not serve the needs of a well trained athlete. Thus, what is a pathologically small laryngeal lumen, with or without pathological adduction during exercise, has not been defined. Concepts like sensitivity and specificity can therefore not be defined within the frames of the present study. We solved this issue in the work with paper # 2 of the present thesis by empirically defined cut-off values. Thus, presently a laryngoscopic “gold standard” that unequivocally defines EILO has not been developed.

9.2.4 Laryngoscopy at rest

In the typical patient with exercise induced laryngeal obstruction in the present study, larynx appeared normal at rest (paper # 2).

Different breathing exercises and provocation techniques have been proposed in order to reproduce symptoms of EIIS without having to perform an exercise test (Christopher & Morris 2010). If successful, such manoeuvres would facilitate laryngoscopic documentation during ongoing symptoms with the patient in a resting position. Suggested techniques include rapid deep breathing, maximum voluntary ventilation (MVV) manoeuvres, panting, sniffing, coughing and various speak tasks.

In our experience, these manoeuvres may successfully reproduce symptoms in some but far from all patients, and they cannot reproduce the clinical context in which the patients experience their problems. Thus, in our opinion this approach is clearly inferior to real exercise testing.

9.2.5 Post exercise laryngoscopy

Post exercise laryngoscopy has been the most commonly applied diagnostic approach in patients with EIIS. Intense shortness of breath, discomfort, dyspnoea, anxiety or panic reactions elicited by the laryngeal obstruction certainly complicates or totally prevents the introduction of the laryngoscope in symptomatic and distressed patients.

There are additionally three circumstances that complicate post exercise laryngoscopy: (1) After stopping of exercise, the minute ventilation falls rapidly (McArdle et al. 1995). (2) Symptoms of EIIS usually peak at maximum ventilation and often resolve rapidly thereafter. (3) At least 1-2 minutes are required to introduce a laryngoscope in any patient. Taken together, post exercise laryngoscopy may end up being performed when the patient is gradually becoming free from symptoms. This may lead to false negative conclusions. We argue that this may explain some of the reports in the literature, e.g. the findings of Newman et al. that laryngoscopy was diagnostic in only 60% of cases (Newman et al. 1995).

Furthermore, if the laryngoscope is successfully introduced before the symptoms have resolved, what may be observed in the patient is an end-result of a long process that started early in the exercise session. What is being seen at this stage in many patients are adducted supraglottic structures and adducted vocal cords accompanied by stridor and respiratory distress and a varying extent of anxiety or panic reaction. This scenario may easily be interpreted as paradoxical vocal fold motion in a hysterical patient. This may be correct, but it is also possible that adduction of supraglottic structures was the primary events and that the vocal fold adduction as well as the panic reaction was secondary phenomena. Thus, post exercise laryngoscopy entails a high risk of making the classical mistake of *reverse causality*; i.e. vocal fold adduction and panic reactions may not be causally related to EILO, but caused by EILO.

9.2.6 The Continious Laryngoscopy exercise test

The Continuous Laryngoscopy Exercise test is the first method by which continuous visualization of the larynx during exercise has been successfully performed with the patient running on a treadmill. The method facilitates continuous review of the changing dynamics of laryngeal structures in all phases of the respiratory cycle and of the exercise session, with simultaneous objective measurements of gas exchange and of the exercise intensity. Video recordings of the larynx and of the upper part of the body and recordings of breath sounds can be recorded and stored for later evaluation and analysis.

We used the same predefined incremental ergo-spirometry treadmill protocol in all patients (Cumming et al. 1978). Hearth rate and parameters of gas exchange were recorded with the ”breath by breath method”. Variables of gas exchange, ventilation and maximal work capacity were recorded as described in the methods section (chapter 6.4.3.). The test procedure was well tolerated. The laryngeal video recordings, the external video recordings, the audio recordings and the ergo-spirometry were technically adequate in most of the 166 patients.

Some would argue that the CLE-test is unnecessary complex and too resource intensive. In order simply to confirm or exclude adduction of laryngeal structures during exercise, hand-held laryngoscopy on a stationary bike or on a treadmill would probably be adequate, without the external video, the sound recording and the ergo-spirometry. However, we argue that as a minimum, the larynx should be visualized from the beginning of symptoms and throughout subsequent development of the exercise session, thereby properly identifying the structures inciting and perpetuating the obstruction. Video and audio recordings should be stored for later reviews and exact analyses. Estimates based on approximate visual impressions, are in our opinion scientifically and clinically inadequate.

The CLE-test meets all these requirements. Firstly, the information is stored and may be reviewed in retrospect in a blinded fashion and also presented to colleagues or other researchers. The ergo-spirometry provides an opportunity to relate symptoms and visual findings to ventilatory parameters. That is, the CLE-test may relate laryngeal obstruction to the breathing pattern of the patient and also assess the extent of ventilatory limitations occurring at the laryngeal as well as the bronchial level of the airway tree. As an example, we have used the CLE-test to measure the effect of intervention in a study of patients with severe and disabling supraglottic EILO treated with laser supraglottoplasty (Maat et al. 2007).

However, until now the full potential of the CLE-test has not been explored.

9.2.7 Mode of exercise used to reproduce symptoms of EIIS

Treadmill running, ergometer cycling or stair climbing have all been used to reproduce symptoms of EIIS (Bent, III et al. 1996; Christopher 2006; Rundell & Spiering 2003; Tervonen et al. 2009). Ideally, the mode of exercise should be tailored to the individual patient, based on triggers identified from the medical history. In a laboratory setting one must compromise and select a practical type of exercise that most children and young adults are comfortable with. Thus, ergometer cycling and treadmill exercise is commonly used. Space requirements clearly favour a bicycle to a treadmill. The cycle ergometer also has a clear advantage compared to treadmill exercise in that the laryngoscope relatively easy may be manually held in correct position during the exercise. There are less movements of the head and of the upper part of the body during cycling than running, facilitating easier and better video-recording conditions.

More important than the mode of exercise, is that the test protocol must ensure a gradually increasing exercise intensity, and also must ensure that subjects reach their maximum exercise capacity. If patients stop before exhaustion, symptoms may not be elicited and the test therefore unsuccessful. In most young people and fit adults, treadmill exercise is a better device than bicycle when exhaustion is the major objective for the test (Garcia de la et al. 1998; Åstrand PO et al. 2003). Despite the challenges involved in securing the laryngoscope to the head of a running subject, we therefore decided at an early stage to use treadmill as the mode of exercise for the CLE-test. Tervonen et al. used an ergometer bicycle in their study, and were unable to reproduce symptoms in 50% of patients and made positive findings in the larynx in 30%, demonstrating the importance of reproducing symptoms when laryngoscopy is performed for diagnostic purposes in patients with EIIS (Tervonen et al. 2009).

9.2.8 Ergospirometry in relation to diagnostics of EIIS

In paper # 1 we describe that exercise flow volume loops (extFVLs) recorded at high intensity exercise in patients with EIIS were positioned closer to total lung capacity (TLC) than expected, i.e. that end expiratory lung volume (EELV) was increased and end inspiratory lung volume (EILV) was decreased compared to control subjects, suggesting dynamic hyperinflation. This finding was also observed in several patients participating in paper # 2. A gradual leftward shift of the extFVLs was observed in parallel to increasing symptoms of EIIS. This observation seemed relatively consistent, and was initially interpreted as a sign of dynamic hyperinflation. However, correct positioning of extFVLs within the maximum flow volume loop requires the test subject to inhale correctly and fully to TLC. Thus, the finding is likely to be related to the difficulties experienced by patients with EIIS to inhale fully during exercise, thereby erroneously positioning the extFVLs closer to TLC (Sietsema & Porszasz 2007).

In many of the patients of the present study, a truncated inspiratory part of the extFVLs was observed to develop in parallel with increasing shortness of breath and symptoms of EIIS. This has also been described by others (Christopher et al. 1983; McFadden, Jr. & Zawadski 1996). Truncated inspiratory extFVLs must represent abrupt changes of flow velocities. One may therefore speculate that this finding may be a sign of abnormal laryngeal function, quickly obstructing and thereafter reopening the lumen. This issue has not been investigated in studies.

Normally, laryngeal resistance is slightly lower during inspiration than during expiration. Correspondingly, the time ratio between inhalation and exhalation is approximately 40-60. Theoretically, inspiratory obstruction would influence this time ratio and prolong the inspiratory phase (Johnson et al. 1999). Thus, the relation between inspiratory and expiratory time could theoretically be used in the diagnostic work-up of patients with EIIS. This approach has not been assessed in studies.

In summary, exercise flow volume loops and parameters of gas exchange during exercise may potentially aid in the diagnostic work-up of patients with EIIS but little scientific work has so far been done, utilizing objective test methods to verify diagnostic sensitivity and specificity.

9.3 Laryngoscopical findings in relation to EIIS

9.3.1 Normal larynx response to exercise

The findings in the asymptomatic control subjects participating in the present study basically confirmed previous findings that the larynx normally opens widely and that the epiglottis rotates anteriorly into the base of the tongue during exercise (Bent, III et al. 1996; England & Bartlett, Jr. 1982; Hurbis & Schild 1991). These adaptive changes allow for increased airflow without major increases of laryngeal resistance (Beaty et al. 1999; England & Bartlett, Jr. 1982; Hurbis & Schild 1991). Also, the mild medial rotation of the cuneiform tubercles observed in 40% of our control subjects has been described in subjects without respiratory complaints (Bent, III et al. 1996). For the purpose of the present study, this finding was therefore considered normal. Since this decision was based on relatively few observations, it cannot serve as a validated cut-off for what is to be considered a normal laryngeal response to exercise. This issue must be explored in much larger studies of subjects without exercise related symptoms.

9.3.2 Diversity of findings in subjects with EIIS

We were unable to link symptoms of EIIS to one single structure or causal factor. However, in the typical patient, larynx appeared normal at rest. Contradicting previous statements in the literature, a primary adduction of the vocal cords was not a major inciting factor, but in most patients rather a consequence or an associated phenomenon occurring secondary to supraglottic obstruction. Clinical symptoms seemed to progress in a continuum and in parallel to an increasing medial rotation of the cuneiform tubercles and inward movement of the aryepiglottic folds. Obvious stridor was in most cases related to adduction of the vocal cords, and panic reactions to more pronounced vocal cord adduction. The time throughout the exercise test from the onset of clinical symptoms to audible stridor could be heard, varied considerably between subjects.

In most previous literature, symptoms of EIIS have been understood as signs of vocal cord dysfunction or VCD. Our findings indicate that this is not correct. Only 4 (2.6%) of 151 patients had a primary VCD, as defined by Christopher (Christopher et al. 1983). These findings are supported by similar findings from Nordang et al. (Nordang et al. 2009). Using the definitions of Brugman and Kenn, nearly every patients complaining of EIIS should have VCD. The term VCD directly points to anatomical structures that are not primarily involved in most patients. In our opinion, it should therefore not be used. The underlying psychological connotation that has been linked to the term VCD further emphasizes the need for a new taxonomic system.

Thus, it should be stressed that stridor during exercise must not be linked to one particular anatomical structure, pathophysiological process or diagnostic entity. Recognizing this, treatment must obviously be individualized and based on the findings in each and every patient. One cannot simply treat patients with symptoms resembling EIIS as if they all suffer from one diagnostic entity, an approach that has been applied in most scientific studies until recently. In December 2011, Pediatrics published a paper from Harvard Medical School diagnosing paradoxical vocal fold adduction in 60 patients based on presenting symptoms alone (Maturo et al. 2011). The authors argued that laryngoscopic confirmation of the diagnosis was unnecessary. Our findings do not support this opinion.

We acknowledge the possibility that our patient population may have been biased in that we basically recruited from an outpatient pediatric lung clinic, and mainly subjects complaining of exercise induced symptoms. The literature in this field does not discriminate properly between studies that include patients on the basis of a wide variety of triggering factors. Thus, smaller studies of patients referred to third level laryngology departments may therefore conclude differently from our relatively broad study of otherwise well functioning adolescents. Having said this, more studies using laryngoscopy during ongoing symptoms is required to solve this discussion. Therefore, in our opinion, Maturo et al.(Maturo et al. 2011) are mistaken when they argue that laryngoscopy is unnecessary when examining patients with EIIS.

To assess the sensitivity and specificity of a test, it must be compared with some reference test (the best test available) or a ”gold standard”. Laryngoscopy during ongoing symptoms has been proposed to be such a ”gold standard”, confirming the presence or absence as well as the characteristics of EILO. Our findings reveal a complex picture of findings in patients complaining of symptoms resembling EIIS. Laryngoscopy provides a good visual picture of the response of the larynx to the exercise, but do not presently represent a ”gold standard” in the scientific meaning of the word, since there is currently no consensus regarding the limits for the extent of adduction required for a positive test. There are only two methods published that objectively attempts to describe the extent of laryngeal obstruction in patients with EIIS, the EILOMEA and the Maat-score (Christensen et al. 2010; Maat et al. 2009; Roksund et al. 2009). Both methods are based on rater-selected images of the maximum laryngeal obstruction when the patient is close to exhaustion. Defining EILO based on both of these methods, Christensen and co-workers described an incidence of EILO of 7.5% in a population based cohort of young subjects from Copenhagen (Christensen et al. 2010; Maat et al. 2009).

In paper # 2, we demonstrated that 23 subjects with symptoms of EIIS had mild or no adduction of the laryngeal structures. This indicates that it may not only be the extent of the adduction per se that is related to laryngeal obstruction. Airflow capacity through the larynx should probably be related also to the absolute and baseline size and shape of the laryngeal lumen. Thus, a small degree of adduction in a subject with a wide larynx may have a different consequence for airflow resistance than the same extent of adduction in another subject with a more narrow larynx. This cannot be sorted out using video assessment alone, but will require the use of pressure and flow measurements inside the laryngeal lumen.

9.3.3 Laryngeal effects from exercise in patients with left vocal cord paralyses

A study of adolescents and young adults with a history of extremely preterm (EP) birth was running in parallel to the present study in the Pediatric Cardiopulmonary Test Laboratory during the period 2001-2009. Exercise testing constituted parts of the test program that was applied in that study. It became apparent that two of these patients had exercise induced inspiratory symptoms that were similar to those of patients with exercise induced laryngeal obstructions. Also, patients recruited into the "EIIS-study" were diagnosed with unilateral vocal cord paralysis, one of whom was an ex-preterm with left sided vocal cord paralysis (LVCP). A literature search revealed that LVCP was a well-established complication of surgical treatment of patent ductus arteriosus (PDA) in EP born infants. It was argued in the few articles studying this condition, that LVCP should not be accompanied with long-term negative consequences, since the functioning right vocal fold would adjust to the situation and prevent symptoms.

However, this issue had not been addressed in research, since studies including and assessing patients after early childhood had not been performed. We therefore searched the medical records for information regarding surgical treatment of PDA in all subjects participating in the parallel follow-up study of EP born subjects. We found 13 subjects with this history in a cohort consisting of 46 (91%) actually participating subjects out of 51 eligible subjects. We performed laryngoscopy in 11 subjects and diagnosed LVCP in seven. All these seven subjects were evaluated for a CLE-test, which for various reasons was performed in only three. An increasing anteromedial rotation of the left cuneiform tubercle and the left aryepiglottic fold was observed in all these three subjects, as the exercise session proceeded. At maximum exercise, the left supraglottic structures severely compromised the laryngeal entrance. As viewed through the laryngoscope, the airflow had to follow an increasingly twisted pathway through the larynx to enter the lower airways. Findings varied slightly between patients, and we do not feel confident that the mechanism(s) of injury are similar in all patients.

In this paper we have established that laryngeal injuries that are related to surgical treatment of PDA in EP born infants last until early adulthood and may be permanent. This observation should be taken into account when treatment strategies for EP born children with PDA are contemplated. Today, a more restrictive attitude to treatment of PDA seems to gain ground. If treatment is required, a pharmacological alternative exists, although this option carries its own potential side effects, and also may relatively often not be successful. Furthermore, a diagnosis of LVCP must not be forgotten or confused with other diseases throughout childhood, such as epilepsy, apnoea attacks, cardiac dysrythmias or asthma, as was the case in several patients participating in our relatively small study.

We have also suggested that further studies are required to establish what mechanisms of injury might be involved. Injury to the left recurrent laryngeal nerve seems the most plausible mechanism. However, in one of our patients it was explicitly noted in the medical records that this nerve had been observed and avoided during the surgical procedure. Nevertheless, that patient developed a LVCP. Neural injuries unrelated to surgery itself may therefore be involved, such as harmful effects from a large and pulsating PDA. In addition, mechanical injuries to the larynx itself cannot be excluded.

In this article we conclude that laryngeal function should be focused on after EP birth if a large PDA has been observed during the course of the neonatal period, and particularly if surgical treatment has been performed. Laryngoscopy should be performed in such patients if symptoms indicating laryngeal airflow obstruction are presented. More research is required, in order to sort out causal mechanisms.

9.3.4 Age in relation to EILO

Most patients included in this study were examined as adolescents (mean age 16.3 years, SD = 7.3), and most reported that their breathing problems had started in early puberty. Due to the shape of the aryepiglottic folds and the cuneiform tubercles, the supraglottic space is relatively more narrow in teenagers than in adults, (Fried 1996; Wysocki et al. 2008). Also, the epiglottis is relatively long and can be curved or omega shaped (Hast 1970). This relative proximity between the aryepiglottic folds and the elongated epiglottis may reinforce the inward suction induced by the increased inspiratory flow triggered by exercise, as explained by the Bernoulli effect. A coexisting docile or inadequate laryngeal framework may result in anteromedial supraglottic collapse. Continuous movements or vibrations from these tissues may induce irritation that can lead to inflammation and oedema. This may further reduce the supraglottic space, thereby increasing the adducting forces and provide a basis for increasing symptoms. It may be difficult to distinguish between the redness and oedema caused by such mechanical forces and the inflammatory oedema caused by acidic laryngo-tracheal gastric regurgitation.

9.3.5 Gender in relation to EIIS

Several reports have concluded that EILO is more common in girls than in boys (Bittleman et al. 1994; Bjornsdottir et al. 2000; Christopher & Morris 2010; Fahey et al. 2005; Lakin et al. 1984; Morris & Christopher 2010; Smith et al. 1995). In the present study, we also found EILO to be more common in girls; i.e. 99 (66%) the 151 included patients with EIIS and 81 (71%) of the 113 patients with verified EILO were girls. Mean age was 16.2 years for the girls and 16.4 for the boys. It is relevant to ask why the rate of occurrence varies between male and female adolescents of similar ages. One possible explanation may be a varying laryngeal anatomy between males and females at this age. Anatomical studies have revealed no sex-related differences regarding the size of the laryngeal opening during the pre-pubertal years. However, a significant sex difference regarding laryngeal dimensions has been observed throughout the pubertal growth spurt (Castelli et al. 1973; Wysocki et al. 2008). Explained within the framework of the Bernoulli effect, a smaller laryngeal opening creates a greater inward suction at any given airflow and thereby a greater tendency for collapse. Also, the supporting structures of the adolescent female larynx may be different from that of the males, possibly related to hormonal factors (Fried 1996). The growth of the length of the pharyngeal cavity and of the nasal opening has been shown to differ between males and females throughout puberty, possibly adding further load to a disadvantageous flow through the female larynx.

9.3.6 Validity of findings in relation to EIIS and EILO

Validity generally refers to the extent to which a measurement corresponds accurately to the real world. Transformed into a test situation, validity expresses whether or not the method is suitable as a measuring instrument and whether it measures or predicts what is the basis of the problem of interest. The concept of validity may be split into an internal and external part. Internal validity indicates the extent to which the researcher controls all the variables that can affect the result. External validity indicates to what extent the results can be generalized (Thomas & Nelson 1990).

The aim of the study presented in paper # 3 was to establish and validate a clinical score system for laryngeal obstruction in patients with symptoms of EIIS, as this can be observed by continuous laryngoscopy during exercise. We wanted to assess the extent to which the score system reflected the symptoms as they were reported by the patients, and the extent to which the score system corresponded to the extent of the distress, as scored by a blinded observer. The significant and strong positive correlation that was observed between respiratory distress and laryngeal adduction during exercise strengthens the argument that laryngeal obstruction is an important causal factor for the symptoms of the patient. One should, however, be aware that the performance during the test, as well as the subjective perception of the distress, probably are influenced by factors such as skills, attitudes to exercise, expectations and personal goals. In line with this, we observed some young athletes who continued running despite severe symptoms of distress, while other subjects stopped early with seemingly minor symptoms. Also, some patients stopped exercising with low CLE-test scores in parallel with relatively higher scores of subjective complaints. This may be a sign of lack of validity of the CLE-test score, i.e. the score system may not measure what constitutes the problem of the patient. However, these issues are difficult to penetrate within the framework of the present study. Particularly the interface between health and disease are influenced by these mechanisms. Thus, subjects with a “near-normal” larynx who complains easily as well as subjects with an “apparently deviating larynx” who easily tolerates hardships, contribute to the blurring of the line of normality. To sort out these issues, a much larger population needs top be examined, particularly a larger population without symptoms of EIIS. In the present study, we found that patients with EIIS could be separated from symptom negative control subjects by a CLE-test sum score cut-off point of three. A more robust cut-off for what should be regarded as healthy laryngeal function during exercise requires a study that includes more subjects without symptoms resembling EIIS. An example that illustrates this point, was the finding that supraglottic adduction at moderate effort differed between patients and controls, but when age and gender were included in the statistical analyses, this difference was not significant. On the basis of this, it may be argued that a subtle adduction of the aryepiglottic folds early during an exercise session may be a normal phenomenon and also more dependent on age and gender than the other sub-scores.

Maschka et al. have proposed a classification of disorders relating to exercise induced stridor, in which two out of seven causes were either psychological or related to personality traits like factitious, malingering, somatization or conversion disorders (Maschka et al. 1997). Thus, one may argue that psychological factors can affect and interact with the perception of symptoms, complicating a straightforward assessment of the association between objective findings in the larynx and subjective complaints.

The relationship between EILO and EIIS was clearly demonstrated in a study of Maat et al., in which 10 patients who suffered from what was assumed to be severe supraglottic EILO underwent endoscopic supraglottoplasty (Maat et al. 2007). The typical severe adduction of supraglottic structures in parallel to severe inspiratory stridor was observed preoperatively in all patients, but could not be observed postoperatively in any of the patients. Disappearance or significant improvements of symptoms of EIIS after surgical removal of supraglottic structures strongly points to the supraglottic structures as the causal factors.

Regarding external validity, any population bias would be of importance. As stated in chapter 8.3.2, most patients included in the present study were otherwise healthy and active adolescents, recruited from an outpatient pediatric pulmonology clinic in the second largest Norwegian city. The extent to which our findings are representative for all types of patients with periodic occurrence of laryngeal obstruction (POLO), cannot be answered before more studies are done also in other types of populations, utilising objective test methods.

9.3.7 Repeatability

Repeatability and reliability are concepts that may be used interchangeable. Inter-observer repeatability addresses if a test provides the same results regardless of who carries out the measurements. Intra-observer repeatability addresses if a test provides the same results when assessed twice or more by the same observer. Intra-subject repeatability addresses if a test provides the same results if carried out twice or more in the same subject under the same conditions (Altman 1995; Thomas & Nelson 1990). This requires that the physical fitness or the health condition of the subjects do not change between the measurements.

Important factors in the context of repeatability are the experience of the test leader, the environmental conditions during the test and the stability of the protocol according to which the exercise session is run. High repeatability is achieved if random errors are small and few. Repeatability is an integrated part of validity. A test can be repeatable or reliable without being valid, but it can not be valid if it is not reliable (Altman 1995; Thomas & Nelson 1990).

In the present study, inter-observer and intra-observer repeatability of scores was found to be adequate. Since the method for CLE-test score is new, a better specification of the boundaries between the different scores and better training of those scoring, may improve the results. We concluded in paper # 3 that the CLE-test score system provided a reliable and valid tool to differentiate abnormal from normal laryngeal observations during exercise. However, the instrument should be compared with alternative methods and also applied in larger population studies in order to clarify aspects such as sensitivity, specificity and predictive values.

We have not assessed intra-subject repeatability in the present study. This must be done in order to identify what might be significant changes from interventional measures or studies, such as treatment protocols.

9.4 Causal aspects related to EILO

There must be a threshold for how much air that can flow freely through the larynx. The Bernoulli effect teaches us that increasing airflow through a tube leads to increasing negative pressure within the tube. Depending on the airflow velocity and the strength of the supporting structures, sooner or later the tube will collapse. The level of flow that the larynx can withstand will logically depend on the size of the laryngeal opening and the stability of lateral laryngeal structures. Also, as turbulence increases the negative intra-luminal pressure, the configuration of the laryngeal entrance may also play a role. Fahey et al., reported that supraglottic EILO occurred only near peak exercise, and not as progressive findings during the exercise session (Fahey et al. 2005). This does not fit our experience. Despite large inter-individual differences, a slow onset of respiratory symptoms in parallel to gradually increasing medial movements of supraglottic structures was observed in most patients.

Supraglottic EILO is associated with a clearly visual and measurable narrowing of the entrance of the larynx (Christensen et al. 2010). By Bernoulli's law, the negative pressure during exercise will be at its greatest in this area, increasing the relative contribution of the upper airways to the total respiratory resistance, and also promoting an inspiratory collapse of supraglottic structures (Ferris et al. 1964). What local laryngeal factors that predispose certain patients to this scenario, are mostly unknown. Somehow one would expect the larynx to be poorly supported or that muscles, ligaments or the laryngeal cartilages are structurally abnormal. It has been speculated whether there is a correlation between infantile laryngomalacia and EILO. However, to our knowledge, only one patient has been described in the literature suffering from EILO who also had a history of laryngomalacia in infancy (Mandell & Arjmand 2003).

We found that paradoxical adduction of vocal cords usually developed after adduction of supraglottic structures (88 of 113 patients). Similar results have been described (Nordang et al. 2009; Tilles & Inglis 2009). A weakness in the abducting muscles or of the supporting structures that stabilize the arytenoids and keep them in an upright position, may explain the primary supraglottic obstruction observed in most patients. If the arytenoids are not kept upright, the vocal processes will turn downwards and inwards. This will reduce the size of the laryngeal entrance to less than the critical diameter required for laminar and advantageous aerodynamic inspiratory flow (Fink BR 1975). Fatigue of abducting muscles of the larynx may also be involved in this scenario, favouring the forces acting inwards. A secondary paradoxical medial motion of the vocal cords may be explained by pressure changes in the space between the vocal cords, due to changes of airflow induced by medial movements of the structures above (Fink BR 1975).

Only 4 of 113 patients in the present study had a pure VCD with an unambiguous primary glottic obstruction. There is reason to speculate that the symptoms and the EILO presented by these four subjects may be related to pathological mechanism that differ from the majority of our patients

9.4.1 Hyperreactivity and changes in reflex interaction

Reflexes play an important role for laryngeal function in relation to respiration, swallowing and the protection of the airway from aspiration. The hypothesis explaining the concept of "reflex associated VCD" is that direct stimulation of sensory nerve endings in the upper or lower respiratory tract may stimulate local reflexes, leading to laryngeal closure (Perkner et al. 1998). Mechanical or chemical stimulation of the supraglottic mucosa or direct stimulation of the superior laryngeal nerve may activate the laryngeal adductor reflex to protect the airway from aspiration or asphyxiation (Thompson 2007). A varying sensitivity or intensity of this reflex interaction in the larynx may lead to a corresponding varying threshold for laryngeal closure. Conditions such as allergies, reflux and infections may alter this reflex interaction.

Despite the hypotheses of "reflex associated VCD" there is little objective evidence defining the specific role of laryngeal hyperresponsiveness or the alterations of the autonomic balance that should lead to VCD.

9.4.2 Laryngopharyngeal reflux (LPR)

Gastroesophageal reflux disease (GERD) has been linked to VCD by several authors (Goldberg & Kaplan 2000; Harding et al. 2000; Kenn & Balkissoon 2011; Koufman et al. 2002; Maschka et al. 1997; Morrison et al. 1999; Perkins & Morris 2002; Tilles 2003). The argument has been that acidic reflux reaching the laryngopharyngeal area should induce some form of hyperexcitable state (Balkissoon 2002; Kenn & Balkissoon 2011; Morrison et al. 1999; Yelken et al. 2009). According to the conclusions of Mathieu, laryngeal findings in LPR are non-specific and difficult to distinguish from other causes of upper respiratory tract inflammation (Mahieu 2007). Unpublished data from the present study indicate that some extent of redness and signs of laryngeal oedema could in fact be observed in some patients. However, these findings were not analysed formally. In our view, it is difficult to distinguish between redness due to mechanical vibrations related to the EILO itself and redness due to acidic reflux.

A putative association between LPR and VCD should be verified using objective methodology in controlled studies, including pH measurements in the laryngopharyngeal area. Also, one would expect that treatment with proton-pump inhibitors (PPIs) would be of help in these patients, regarding reflux related symptoms as well as symptoms related to EILO.

Cukier-Blaj and co-workers recently published an interesting study, indicating that subjects with a high reflux symptom index (RSI) in fact had reduced laryngeal sensitivity (Cukier-Blaj et al. 2008). They used an objective test method to assess laryngeal sensitivity, identifying the threshold of the laryngeal adductor reflex. An increased stimulus was required to release this reflex in patients with a high reflux symptom index. These findings do not support the theory that GERD should be related to laryngeal hyperexcitability and thereby explain VCD or EILO. A recent study by Maturo et al. support these findings (Maturo et al. 2011). They describe that seven of 59 patients with diagnosis of paradoxical vocal fold motion were referred for pH probe measurement and four had evidence of GERD. In three of these four patients, PPIs was started with no effect on the symptoms of paradoxical vocal fold adduction Speech therapy, however, applied in these same patients, improved their symptoms. More studies need to be done with PPI treatment in patients with LPR before its relation to EILO may be clarified.

9.4.3 Psychological aspects and EILO

Historically, there has been a strong tendency to interpret VCD within a psychological paradigm. In their review article, Leo and Konakanchi found that out of a sample of 171 cases with paradoxical vocal cord motion (PVCM), only 7% did not have a psychiatric diagnosis (Leo & Konakanchi 1999). Others have claimed that VCD is associated with conversion disorders, representing the physical manifestation of underlying psychological problems (Husein et al. 2008). In our study, patients were not exposed to formal psychiatric assessment. However, based on decades of experience from working with children and adolescents, we found no reason to suspect that the majority of the included 166 patients should suffer from any kind of psychiatric diseases. It was our impression that most of these patients were otherwise healthy and physically active adolescents who needed to be explained that their breathing problem was not dangerous and that there was nothing mentally wrong with them.

However, we could observe that many of our patients were concerned and sometimes frightened by their symptoms, and also sometimes hesitant in relation to exposing themselves to situations that they knew would provoke them. In our opinion this reaction was understandable, considering the trauma of experiencing breathlessness during heavy exercise. The panic reactions that could be observed in some of them should generally not be interpreted within a psychiatric context but as a normal and natural response to the occluded airways.

We do not exclude the possibility that stress, anxiety and a competitive personality may worsen and possibly also trigger symptoms and findings, but argue that there is an organic laryngeal substrate making the EILO response possible in the majority of patients (Ommundsen et al. 2006). Also, we cannot exclude that psychiatric disease and conversion disorders may be a triggering mechanism in some patients, but in our experience these were not diagnoses that were present in the majority of patients included in the present study. Biased sample populations may of course explain some of the different conclusions that are reached by the different researchers. We cannot conclude on these issues from the present study, since formal psychological and psychiatric assessments were not performed. However, it seems pertinent to comment in this context, that studies concluding that psychiatric diagnoses are highly prevalent in this group of patients, generally diagnose "paradoxical vocal cord adduction" with inappropriate methods (Maturo et al. 2011). We argue that both the laryngeal and the mental assessment need to be done with appropriate methods in unselected populations with EIIS.

9.4.4 Environmental conditions and EILO

In exercise-induced asthma, temperature and humidity are important factors that are involved in the pathogenesis. In the present study, there were some activities that seemed to be more often involved as triggers of symptoms of EIIS. Thus, subjects involved in winter sports such as cross-country skiing, biathlon and alpine skiing seemed to be over-represented, as were swimmers, handball and soccer players. Most patients explained that cold weather usually reduced the tolerance to exercise. These findings correspond partly to the descriptions given by Rundell and co-workers, reporting that inspiratory stridor was more prevalent in outdoor athletes (8.3%) than in indoor athletes (2.5%) (Rundell & Spiering 2003). These findings suggest that environmental factors may affect the occurrence of EIIS as in EIA.

9.4.5 Athletic fitness and EILO

Bent and co-workers hypothesized that well-trained athletes, who could generate high airflow through the larynx for a longer period of time, were more likely to get EILO (Bent, III et al. 1996). Beaty et al. argued that EILO was related to high inspiratory air flow, and that physically active people were therefore more likely to be affected (Beaty et al. 1999). This corresponds well to what was observed in the present study. Different sports have different demands in relation to maximum ventilation, respiratory frequency and ventilatory rhythm. It is normal to adapt the breathing pattern to the movements required by the sport performed. Endurance sports require large ventilatory minute volumes, and it seems that the ideal breathing rate in terms of minimizing dead space ventilation is approximately 50 breaths pr. minute. Rowers rarely row at a rate exceeding 40 strokes per minute. Swimmers have very little time to inhale above the water. In addition, they breath rate is usually slow, particularly at short distances. Slow breath rates and short inspiratory times necessarily must lead to an increase of airflow, possibly explaining some of the EILO observed in swimmers. A large proportion of our test subjects had moderate to severe supraglottic adduction already at approximately 80% of their estimated maximum heart rate. About 20 of the participating subjects of the present study were athletes at top national or international levels. One may speculate if these subjects would have had their breathing problems, had they not been elite athletes.

9.5 Prognosis of EILO

The relationship between age and EILO seems more complex than only a matter of laryngeal development. It has been suggested that laryngeal growth and maturation during puberty will overcome the tendency for inspiratory laryngeal collapse during exercise (Zalzal et al. 1987). According to this theory, adolescent growth should make the laryngeal structures more robust and resistant to the inward forces that act during high flow ventilation, and patients should therefore outgrow their condition. However, a 2-5 years follow-up study of patients included in the present study has demonstrated that growth by itself does not cure supraglottic EILO (Maat et al. 2011). It was also noted in that study, that patients reported less symptoms as well as a reduced level of physical activity. It may therefore be that over time, patients adapt to their abilities and adjust their physical activity to a level that is not compromised by laryngeal airflow limitations. However, a reduced level of physical activity was also noted in patients who had been treated with laser supraglottoplasty and therefore had no signs of laryngeal adduction during exercise. These issues are complex, therefore, and cannot be solved within the frames of this study.

9.6 Treatment of EILO

Treatment of EILO is not a subject that has been in focus of the present thesis. However, our research group has treated patients and published papers where patient selection as well as the line of reasoning in this regard has been based on findings presented in this thesis. In the previous literature, treatment of EILO seems to have been based on the presenting symptoms, as has the assessment of treatment success rates. So far, no studies reporting on various treatment remedies or regimens have acknowledged the variety of central airway pathology that may present with seemingly similar symptoms. Most patients presenting with exercise induced inspiratory symptoms seem to have been treated as if they were suffering from one defined disease entity.

The present thesis has shown that this may be an incorrect strategy, since a relatively wide variety of conditions in the central airways may present with symptoms that may be difficult to distinguish between. Also, extra-laryngeal pathology needs to be excluded, observed in nearly 10% of subjects included in the present study. Few studies have directed the treatment towards objectively verified abnormalities, and posted up a planned treatment strategy targeting this. Speech therapy is the treatment option that is most often used, and also often described as effective. However, in the majority of studies, detailed descriptions of what has actually been done during the speech therapy, are not presented. Furthermore, the issue of treatment success or failure are in most studies addressed using some sort of symptom score, based on subjective assessments with few or none objective outcome measures (Christopher 2006; Newsham et al. 2002; Sullivan et al. 2001). What we need right now, are large prospective randomized controlled studies, with careful classification of patients before inclusion and - to the extent possible - with careful objective assessment of outcome.

So far, surgical treatment of severe supraglottic disease is the only treatment modality in this context where outcome has been assessed with objective methods. Selection of patients for surgical treatment must be performed with great care, particularly avoiding selecting for such treatment, patients who have a primary glottic EILO. In addition, potential gains must be weighted against the risk of potential complications. (Maat et al. 2007; Maat et al. 2011).

10. Concluding remarks and future prospects

In this thesis we have shown that the larynx may safely be studied during ongoing active treadmill exercise to exhaustion. We have shown that exercise induced inspiratory symptoms may be associated with a wide variety of dysfunctions or malformations, mainly located to the larynx and mainly to supraglottic structures. We have presented a system for scoring of severity of laryngeal adduction, correlating adequately with scores of symptom severity. We have also applied the test set-up to subcategories of patients suffering from established laryngeal pathology, such as recurrent nerve paralysis, obtaining knowledge that would otherwise not have been available.

Future studies should be conducted, including large, unselected and unbiased populations complaining of exercise induced inspiratory symptoms, in order to confirm or reject the findings of the present study. Subjects without symptoms of respiratory distress or limitations needs to be studied, in order to establish thresholds for what are expected and normal and what are abnormal laryngeal response patterns to exercise. Within subject test-retest reliability assessment needs to be done in order to establish the stability of laryngeal response patterns and of the measurements, characteristics that are important for the interpretation of intervention studies. Potential influence from the test set-up per se also needs to be addressed, a work we have started. Measurements of pressure and airflow gradients within the laryngeal lumen may be necessary in order to improve our understanding of these issues. Taxonomy and nomenclature needs to be agreed on, and classification systems should be established that are based on international consensus and objective assessments. Presently, nomenclature contributes to confusion, more than to clarification, a situation that needs to be changed. Future studies should follow strict rules for the description of findings and for classification of patients in order to avoid misunderstanding between research groups.

Intervention studies and treatment protocols must acknowledge the diversity of findings that seems to be related to relatively similar symptoms. Outcome measures must be based on symptom descriptions as well as on objective findings in the larynx, involving video recordings, sound recordings, and in the future, hopefully also measurements of airflow velocities and pressure gradients. Ergospirometric data, such as ventilatory patterns and exercise performance, may be developed into important non-invasive outcome measures, however this will require extensive validating studies.

The understanding of the etiology of EILO is inadequate, and so far only speculations have been put forward. Classical mistakes have probably been made over the years, based on observed associations that may not have been causally related or also, where the causal direction may have been the reverse of what has been postulated.

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