Treatment of Exercise-induced Laryngeal Obstruction

Exploring modalities in short and long term

Astrid Sandnes

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2021

UNIVERSITY OF BERGEN

Treatment of Exercise-induced Laryngeal Obstruction

Exploring modalities in short and long term

Astrid Sandnes

Avhandling for graden philosophiae doctor (ph.d.)
ved Universitetet i Bergen
2021

Scientific environment

The work presented in this thesis was carried out between 2011 and 2020 and is based on patients referred for work-up and treatment at a dedicated respiratory outpatient clinic at Haukeland University Hospital Bergen, Norway, consisting of a cross-professional collaboration between Department of Pediatrics and Otolaryngology.

The clinical work with EILO patients was started by my supervisors, and I was invited into this research environment as a medical student in 2010. This was at the very beginning of the systematically work in the “embryonic field” of developing treatment modalities for EILO. Research performed in a clinical setting, focusing on a condition that was poorly described, has certainly been challenging and sometimes “frustrating”, and has led to some limitations. The work has been gradually adjusted as our empirical understanding has developed.

During my work with this thesis, the research environment has established itself as the Bergen ILO Research Group at Haukeland University Hospital.

The supervisors during this work:

Ola Drange Røksund, professor, main supervisor
Thomas Halvorsen, professor
John-Helge Heimdal, professor
Hege Havstad Clemm, MD, PhD
Tiina Andersen, MSc, PhD

Statistical analysis was carried out under the supervision of Geir Egil Eide, Professor at Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway

I was enrolled as a PhD student at the Department of Clinical Science, Faculty of Medicine and Dentistry, University of Bergen, Norway. Innlandet Hospital Trust, Department of Medicine, Gjøvik, Norway, funded the Phd fellowship from June 2018 to May 2020.

Abbreviations

CI:	Confidence interval
CLE test:	Continuous laryngoscopy exercise test
CLM:	Congenital laryngomalacia
EIA:	Exercise induced asthma
EIB:	Exercise induced bronchoconstriction
EIIS:	Exercise induced inspiratory symptoms
EILO:	Exercise induced laryngeal obstruction
EILO-BI:	(The Olin) Exercise induced laryngeal obstruction biphasic inspiration
ELS:	European laryngological society
ERS:	European respiratory society
FEV1:	Forced expiratory volume in first second
FIV1:	Forced inspiratory volume in first second
FVL:	Flow volume loop
GERD:	Gastro esophageal reflux disease
IBA:	Information and breathing advice
IMT:	Inspiratory muscle training
IMET:	Inspiratory muscle endurance training
IMST:	Inspiratory muscle strength training
LCT:	Laryngeal control therapy
PCA-muscle:	Posterior cricoarytenoid muscle
Pi_{max}:	Maximal inspiratory mouth pressure
RV:	Residual volume
SD:	Standard deviation
TLC:	Total lung capacity
TLE:	Therapeutic laryngoscopy during exercise
VCD:	Vocal cord dysfunction

Acknowledgements

First of all, I want to thank all patients, their guardians and the medical students who participated in the included studies. Without your contribution, none of this work would have been possible.

I am forever grateful for the opportunity to be working with the ILO Research group and there are many people to thank for this experience being both educational and fun!

My main supervisor, Ola Drange Røksund, the sole reason for engaging me to research and my big inspiration. From the first time we talked about the larynx in 2009, to almost daily talks the last year; you have always been available, supported me and thought me everything I know about EILO and a lot about life in general. Our discussions, your feedback and enthusiasm has made me want to spend a lot of my spear time working with EILO. Thank you! I look forward to the continued work, there is so much more we need to investigate…

Another major strength Professor Røksund has is the ability to network, and always focus on collaboration, which has led me to be fortunate to work with many talented people;

Professor Thomas Halvorsen, your knowledge, scientific writing, honest feedback combined with your humor has been indispensable. I am incredibly grateful to have worked with you and I have learned so much from you.

Professor John-Helge Heimdal, your support of this work and your knowledge about the larynx has been an enormous inspiration and a great privilege. I appreciate your timely precision throughout this work.

Associate professor Hege Havstad Clemm, thank you for valuable comments and support, for keeping order in all applications and approvals and for making possibilities happen in this research field. Our discussions on EILO has been much appreciated.

Associate professor Tiina Andersen, I am incredibly thankful for all your knowledge, enthusiasm, humor and valuable comments and also for wanting to collaborate with “just a medical student” in 2010. I value our discussions, both educational and social.

There are many more that deserves to be thanked; professor Trond Markestad for valuable support. Maria Vollsæter, for your appreciated comments and thorough proof-reading, and for talks about the important things in life. Magnus Hilland, for our collaboration, your humor, and valuable comments. Thor-Andre Ellingsen for always answering "yes" and for help with pictures, films and editing. Also, the rest of the team; Lorentz Sandvik, Ingvild Engesæter, Mette Engan, Ida Jansrud Hammer, Merete Engeseth, Merete Benestad Tom Karlsen and Zoë Fretheim-Kelly.

Professor Geir-Egil Eide, thank you for help with overlooking the statistical analysis, for patience and helping me to understand basic statistics.

For personal reasons I moved to the other side; Gjøvik. Thanks to Innlandet Hospital Trust for funding the last period of this work and to my boss, Anne Fagerheim Skaug for being positive and facilitating leave of absence. Moreover, I must thank my office colleagues Ane Inger Søberg and Beate Stokke Solvik for valuable talks and support. To my colleagues at the pulmonary department; Astrid Kravdal, Øystein Stubhaug and Linea Brevik, thank you for teaching me and for cheering!

My parents, Grete and Terje, have always been a great support and inspiration. They have thought me to work hard and to show interest in the patients, thank you! I would also like to thank my friends for valuable support and my in-laws for enthusiasm and valuable feed-back on methodological considerations about my work along the way.

And lastly, to "my" Ola, thank you; for letting me complete this work while the kindergarten was locked down, for never complaining, for helping with my "commas" and for your smile in doing it all. Our two children, Haakon and Eirik are the biggest joy of my life and I thank you for reminding me of that every day! I hope my children will be as fortunate as me to be able to work with such amazing people and have fun while working.

To the Bergen ILO group: to be continued…

Astrid Sandnes
Bergen, 15th December 2020

Summary of thesis

Background: Exercise-induced laryngeal obstruction (EILO) is an umbrella term describing inappropriate and transient closure of laryngeal structures during exercise, causing breathlessness and/or noisy respiration (stridor). EILO is a relatively prevalent entity, affecting adolescents or young adults in all activity levels. The condition has been reported to have a considerable functional impact, particularly as a limitation of physical activity in an effort to minimize the occurrence and severity of inspiratory symptoms. Objective visualization of the laryngeal obstruction and determining the level of obstruction within the larynx (supraglottic and/or glottic) during ongoing exercise is considered gold-standard for diagnosing EILO and seems of importance for subsequent treatment planning. Treatment options are based on weak evidence, with evaluation of different modalities mainly based on subjective outcomes. Information about the diagnosis and breathing advice (IBA) seems to be fundamental elements. Small studies and case reports suggests effect from speech therapy, biofeedback, inspiratory muscle training (IMT) and surgical supraglottoplasty. Robust treatment algorithms and follow-up streams are yet to be established.

Aims: The overall aim of the thesis was to explore improvement of symptoms and laryngeal obstruction in EILO patients treated with IMT and supraglottoplasty in short- and long term. *Study #I:* To investigate laryngeal response pattern(s) during inspiratory muscle training (IMT) in healthy subjects using laryngoscopic evaluation and imaging. *Study #II*: To expand our knowledge and to explore possible effects from inspiratory muscle training in patients diagnosed with EILO. *Study #III:* To investigate the efficacy and safety of laser supraglottoplasty for patients with supraglottic EILO, using continuous laryngoscopy exercise (CLE) tests before and after surgery. *Study #IV:* To assess changes of self-reported symptoms and laryngeal outcomes shortly after IMT, and to compare self-reported symptoms with a control group 4-6 years later.

Methods: ***Study design***: An explorative approach with combined descriptive and quasi-experimental observational design. *Study #I*: cross-sectional study, *Study #II*: prospective pre-post study *Study #III*: retrospective pre-post study. *Study #IV*: follow-up study. ***Subjects and study procedures****: Study #I*: Twenty healthy volunteers examined with laryngoscopy during inspiratory muscle training (IMT). The laryngeal movements were retrospectively assessed from video files. *Study# II and #III*: EILO patients examined with continuous laryngoscopy exercise (CLE)-test before and after a treatment; six-week training program with IMT or supraglottoplasty. Outcome data were self-reported symptom scores and laryngeal obstruction (by CLE-scores from video recordings). *Study #IV*: Two groups were retrospectively identified from the *EILO-register*; one group receiving IBA only at diagnosis, and the other additionally receiving six weeks of IMT (IBA+IMT). Laryngeal outcome was assessed shortly after IMT, and the two groups' self-reported symptoms were compared with a new questionnaire 4-6 years later.

Results: *Study #I:* IMT facilitated laryngeal abduction in the investigated healthy subjects and application of medium intensity resistance seemed superior to higher resistance in opening of the laryngeal aperture. *Study #II*: IMT was safe and the perceived symptoms and laryngeal obstruction improved in subgroups of EILO after IMT, with improvement mainly observed at the glottic level. *Study #III*: Supraglottoplasty improved symptoms and reduced laryngeal obstruction in the investigated patients with predominantly supraglottic EILO and appeared safe in highly selected severe cases. Notably, supraglottoplasty might improve also glottic obstruction in patients with combined supraglottic and glottic obstruction. *Study #IV:* The response rate after 4-6 years was 40 % in the *IBA-group* and 55% in *IBA+IMT-group*. After 2-4 weeks, 23/32 in the IBA+IMT-group reported symptom improvements, associated mainly with glottic changes, contrasting unchanged laryngeal scores in 9/32 without symptom improvements. After 4-6 years, self-reported exercise-related symptoms and activity had decreased to similar levels in both groups. Full symptom resolution was reported by 8/55.

Conclusion: Self-reported symptoms and laryngeal obstruction as observed and rated in CLE-tests can improve in EILO patients treated with IBA, IMT or supraglottoplasty. Heterogeneous responses to treatment were observed and substantiates that EILO is a heterogeneous condition, thus it is unlikely that *one* mode of treatment will work in *all*. Individual treatment and follow-up based on laryngeal findings seems essential.

Future controlled studies with longer follow-up time are needed to establish effects from the treatment modalities applied in EILO patients. This work provides hypotheses that may serve as a basis in doing so.

List of Publications

This thesis is based on four papers, appended at the end. The papers are referred to as "Study #I", "Study #II", "Study #III" and "Study #IV".

Study #I: Laryngeal movements during inspiratory muscle training in healthy subjects

Sandnes A, Andersen T, Hilland M, Ellingsen TA, Halvorsen T, Heimdal JH, Røksund OD.
Journal of Voice on 27th July 2013. DOI: 10.1016/j.jvoice.2013.02.010

Study #II: Exercise-induced laryngeal obstruction in athletes treated with inspiratory muscle training

Sandnes A, Andersen T, Clemm HH, Hilland M, Vollsæter M, Heimdal JH, Eide GE, Halvorsen T, Røksund OD
BMJ Open Sport Exerc Med. 2019 Jan 18;5(1):e000436. doi: 10.1136/bmjsem-2018-000436. eCollection 2019.

Study #III: Severe exercise-induced laryngeal obstruction treated with supraglottoplasty

Sandnes A, Hilland M, Vollsæter M, Andersen T, Engesæter IØ, Sandvik L, Heimdal JH, Halvorsen T, Eide GE, Røksund OD, Clemm HH.
Front Surg. 2019 Jul 31;6:44. doi: 10.3389/fsurg.2019.00044. eCollection 2019.

Study #IV: Clinical responses following inspiratory muscle training in exercise-induced laryngeal obstruction (*Manuscript, submitted*)

Sandnes A, Andersen T, Clemm HH, Hilland M, Vollsæter M, Heimdal JH, Halvorsen T, Røksund OD

Contents

Introduction

Exercise induced laryngeal obstruction (EILO) refers to inappropriate transient closure of the larynx during exercise and is a common cause of exercise induced inspiratory symptoms. The work on removing a psychiatric connotation from this diagnosis has come a long way. Consensus is now established that EILO is a separate entity with symptoms only occurring with exercise as an inducer, and the diagnosis is made by endoscopic visualization of laryngeal structures during exercise. However, managing the patient group after a diagnosis has been established, is currently based on empirical data, and the research field of developing evidence-based treatment of EILO patients is at a very early phase. None of the applied treatment modalities have been investigated in controlled and randomized studies of larger patient groups, and evaluation after treatment has mainly been performed without verifiable outcome measures. (Literature search has been done regularly since October 2010 and for the last time on 1st September 2020).

When we started to systematically explore and evaluate the laryngeal response patterns to different treatment modalities, little was known in this field, and we had to "find our way" based on the understanding at that time. We have now contributed to a new research field and made experiences to generate further hypotheses. This thesis serves as "one brick" to the foundation of developing treatment modalities in EILO.

1. Background

1.1 EILO as a clinical entity

Episodic occurrence of laryngeal obstruction has been described in detail throughout history (Appendix 1). The entity was mostly reported in psychiatric literature [4] before a description of five patients with “uncontrolled asthma” led to the name vocal cord dysfunction (VCD) [5]. Early reports focused on laryngeal obstruction at the glottic level, i.e., inappropriate adduction of the true vocal folds [5, 6]. Exercise recognized as a cause of transient inspiratory collapse of laryngeal structures has been described since the 1990s [7-11].

Despite the condition being known for decades, the research field is still at an early phase with primarily empirically based treatment modalities [6, 12]. Knowledge from different centers are difficult to match, pool or utilize by others due to; confusion in terminology with more than 85 different terms applied [4, 13-15], lack of standards for work-up and diagnostics, and lack of stratification and/or co-mingling symptoms induced by exercise and symptoms at rest caused by a variety of other triggers (psychogenic and irritant) [16, 17]. In 2013, a consensus Task Force was commissioned to improve this situation with members appointed by the European Respiratory Society (ERS), the European Laryngological Society (ELS), and the American College of Chest Physicians (ACCP) [18]. The proposed ERS/ELS/ACCP taxonomy for exercise-induced laryngeal obstruction (EILO), rests on findings made by laryngoscopy performed from rest to peak exercise, a continuous laryngoscopy exercise (CLE) test [18-20]. The taxonomy requires visualization of the level of the obstruction within the larynx, i.e., glottic, supraglottic (or both), and what laryngeal structures incites the adduction.

This thesis focuses on laryngeal obstruction induced by exercise, and ILO or EILO will be used throughout this thesis, also when referring to studies using different terminology. The term *patient* will be used throughout this thesis since the participants were referred to the clinic as patients.

1.2 The site of obstruction: the larynx

1.2.1 Laryngeal anatomy

The larynx is a highly specialized and complex organ, which unfolds and folds cyclically for ventilation [21]. The rigid cartilage skeleton, the forceful ligaments and both abductor and adductor muscles makes larynx's two main tasks possible; to secure an open airway during high volume ventilation, and to protect the lower airways from inhaling harmful objects [22]. These combined and often competing roles require fine-tuned control and rapid functional alterations [23]. 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 (vocal folds) and subglottic levels (Figure 1).

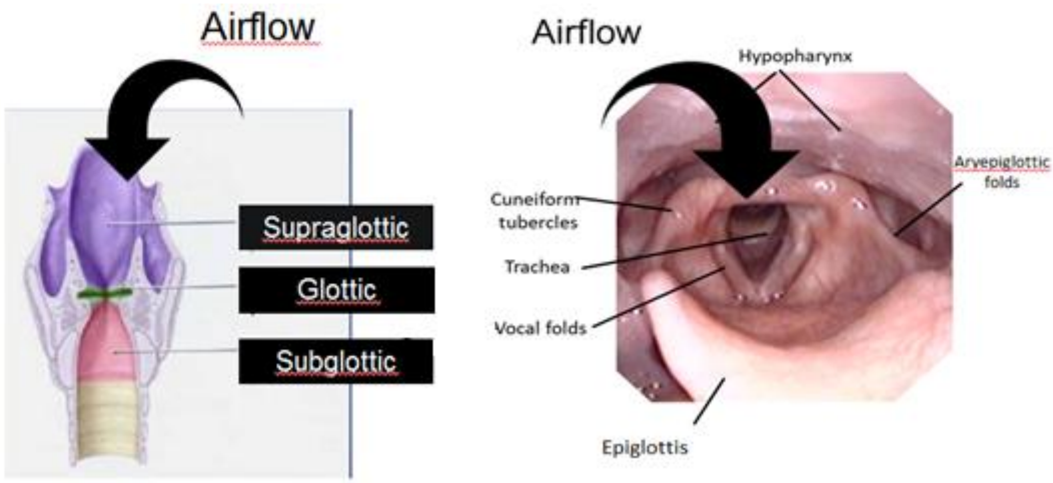


Figure 1: *Overview of laryngeal landmarks and airflow.*

The cartilage framework of the larynx protects from inspiratory collapse and consists of hyaline cartilages; the thyroid, the two arytenoids and the cricoid [24], suspended by muscles and ligaments (Figure 2). The epiglottis is composed of elastic cartilage, with the aryepiglottic folds extending backwards from the lateral margin and medially to the arytenoid cartilages, making a nearly circularly formed margin of the laryngeal inlet [21]. The aryepiglottic sphincter has a solely protective role of the lower airways.

The muscles of the larynx can be divided in extrinsic and intrinsic muscles, all working as an integrated unit [25]. The extrinsic muscles move larynx as a whole, while the intrinsic muscles serve as abductors as well as stabilizers of the arytenoids and the attached aryepiglottic folds, and all act more or less directly on the glottis [23, 25]. The respiratory functions of the larynx are initiated voluntarily but regulated involuntarily. The vocal folds are unique as they are under both autonomic and voluntary control [21-23, 26].

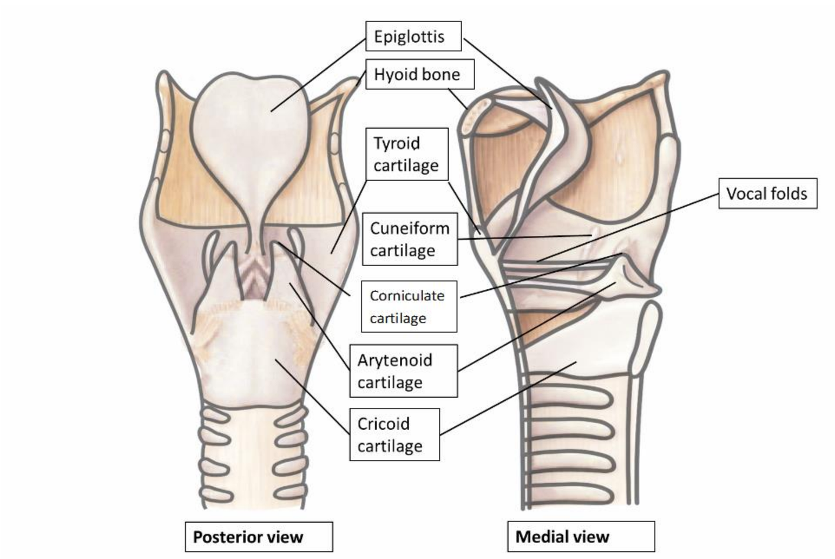


Figure 2: *Cartilages of the larynx*

1.2.2 Laryngeal growth

The supraglottic opening is relatively narrower in adolescents than in adults, with a significantly smaller laryngeal dimension in females than in males throughout puberty [27, 28]. There is an accelerated growth of the vocal folds from 8 to 13 years in both sexes, but the male laryngeal cartilages and vocal folds quantitatively grows more [21, 29]. Also difference in the angle of the two laminae of the thyroid cartilage, respectively 75-90 degrees in adult males and 90 to 110 degrees in females, may affect airflow [21, 22]. The larynx reaches adult size around age 16-17 years [29]. Ossification commonly occurs in the laryngeal cartilages and starts as early as age 20 [21], which may add stability to the musculoskeletal system of the larynx [29]. The ossification may also reduce the flexibility of the larynx, particularly relevant in peak airflow conductance [22]. The growth and gender differences in the laryngeal opening may explain the reported age debut of EILO and the female preponderance seen in most epidemiological studies [30-32].

1.2.3 Larynx as a respiratory organ

Airway resistance

The role of larynx in respiration is primarily to maintain airway patency during inspiration and to keep airway resistance as low as possible [33], adjusted by movements of the vocal folds [34, 35]. Glottis forms the narrowest part of the respiratory tract, and generates turbulence of airflow because of the sharp reduction in airway cross-sectional area [21]. Larynx accounts for approximately 25% of the total pulmonary resistance during mouth breathing (at flow 1 L/s) [24, 33, 36]. During quiet breathing, the glottis opens more widely during inspiration than during expiration, enhancing or decreasing the resistance accordingly [24, 37-40]. Variations in the upper airway resistance is flow dependent as observed during panting and increased flow, which are associated with glottic widening [33, 37].

Vocal fold movement

Vocal fold movements are accomplished by rotation, tilting and anterior-posterior sliding of the arytenoid cartilages and are closely related to the diaphragm and other muscles of the ventilator pump [24]. Medial rotation brings the vocal folds together narrowing or closing the glottis. Opening of the laryngeal inlet is mainly accomplished by the posterior cricoarytenoid muscle (the PCA-muscle), attached posterolateral on the arytenoids, sliding and rotating the vocal processes outward (Figure 3).

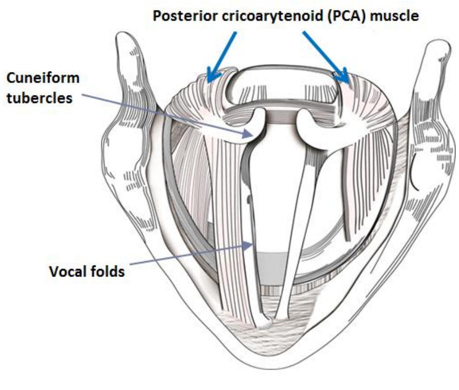


***Figure 3**: Illustration of the posterior cricoarytenoid (PCA)-muscle, the main abductor of the larynx.*

The PCA-muscle is the main abductor of the glottis [39], predominantly active during inspiration and acts in a phasic relationship with the diaphragm activity [21, 23, 41], hereafter referred to as the PCA/diaphragm relationship. The PCA-muscle contracts several milliseconds prior to diaphragmatic contraction, before the onset of inspiratory flow, and its activity continues to a maximum reached approximately in mid-inspiration [37]. By physiological principles, laryngeal resistance must decrease exponentially as PCA activity increases [39]. The cricothyroid muscle tilts the thyroid forward, and when cricothyroid and the PCA-muscles contract simultaneously, a combined lengthening and abduction of the vocal folds occur, making the cross-sectional glottic area larger [23, 24].

1.2.4 Laryngeal function during exercise

The normal laryngeal function during exercise is still not fully mapped out, but is essential in the further study of disease mechanisms in EILO [6, 12, 14]. At high airflow, the vocal folds and the arytenoids move to a relatively fixed abducted position, both in inspiration and also during expiration (contrasting the situation at rest) [8, 38, 42], thereby reducing the upper airway resistance [43]. The abduction continues into the expiratory phase and the larynx appears to play a significant role in determining the respiratory frequency, by determining the duration of expiration [38]. Simultaneously, the epiglottis flattens against the tongue base on inspiration, stretching the aryepiglottic folds allowing for increased airflow [24, 42].

The normal findings have been reproduced in asymptomatic volunteers [11, 44, 45], with some variations. In a study by Beaty and colleagues [42], five of ten asymptomatic subjects significantly increased the laryngeal opening during exercise on a stationary bicycle, while in three the laryngeal aperture did not change. In the remaining two asymptomatic subjects a minor adduction of supraglottic structures during maximum exercise without any glottic adduction occurred. The same minor adduction was also found in 20 asymptomatic volunteers investigated by Røksund and colleagues [11], as well as in healthy controls and adolescents with exercise-induced dyspnoea without a diagnosis (i.e. neither EILO nor exercise induced bronchoconstriction, EIB), in a study by Norlander and colleagues [46]. Thus, some degree of supraglottic adduction may be a normal phenomenon during exercise.

1.3 Exercise and breathing in general

Pulmonary ventilation increases during exercise, induced by the increased metabolic demands of the body. At low intensity exercise, this is accomplished mainly by greater tidal volumes, while at higher intensities, the respiration rate also increases and the expiratory time decreases [38, 43]. The minute ventilation may rise 30 times over resting values, and in top athletes, maximal minute ventilation values of 280 liters per minute has been measured [43, 47]. As the airflow through the airways increases substantially, the turbulence in the upper airways will thus escalate. Athletes shift from predominantly nose to mouth breathing, which alters the pattern of airflow in the upper airways as well as the relative distribution of resistance within the airway tree. Active opening of the mouth tends to widen the laryngeal opening [40].

The respiratory system is put under great stress during high intensity exercise and ideally, breathing is regulated in a way that maximizes the ability to perform. A top athlete demands more of the respiratory system than a recreational exerciser. Anatomy, physiological capacities, and the cardiopulmonary state are important factors contributing to the potential or the limitation of the respiratory system [48]. In addition, each exercise modality/sport has different challenges related to uninhibited ventilation, i.e., optimal conditions for the diaphragm and thorax expansion, dependent on body posture and breathing frequency. Factors such as increased intra-abdominal pressure when running, or the need to combine the motion of thorax expanding and contracting with the rowing stroke movement in rowing, can lead to additional challenges [49, 50]. During swimming, work of breathing is increased due to hydrostatic pressure against which the thorax expands, as well as short time for inspiration. Thus, subjects performing exercise modalities that require additional work from respiratory muscles, might be more susceptible to respiratory muscle fatigue [51]. The larynx also plays a role in some exercise modalities by facilitating elevation of thoracic and abdominal pressure by closure of the glottis [52].

1.4 Aetiological aspects of EILO

The pathogenesis of EILO is not fully understood, and causal theories are mostly based on speculations.

1.4.1 Aerodynamic aspects and breathing pattern

The Bernoulli's principle

As described earlier, the larynx is a narrow part of the airway tree with large variation in resistance. As airflow through the larynx increases with increased exercise intensity, so does the negative inward pressure gradients over the laryngeal opening. The low cross-sectional area of the laryngeal aperture, leads to a pressure-drop that can lead to subsequent progression of obstruction at both glottic and supraglottic levels [8, 53], known as the Bernoulli's principle [10, 54]. Particularly flaccid supraglottic or glottic structures can cause displacement of the air stream, resulting in greater turbulence [55]. Depending on the airflow velocity, turbulence, laryngeal architecture and the strength of the supporting structures, the tube will eventually yield to increased negative pressure within the tube [22, 23, 40, 56].

The critical point of obstruction

A low airflow resistance is obviously important to maintain high ventilation during exercise with a minimum amount of energy expenditure. Thus, coordination of the laryngeal muscles is highly significant when the ventilator requirements are high, and the last fraction of millimeters of glottic enlargement may be crucial [57]. Normally the airflow through the larynx is highest in the posterior part of the glottic aperture, when the dorsal parts of the vocal folds are lifted cranially [58]. The critical point of obstruction of the larynx required to produce symptoms in any given individual is difficult to assess, and probably depends on the timing of the breathing cycle, the airflow, the absolute size of the larynx or other individual differences [4].

According to the law of Poiseuille, a reduction of the radius of the laryngeal opening will increase resistance to airflow by the fourth power of the radius. Therefore, 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 narrower larynx. We have no knowledge on what are the normal or optimal relations between body size, ventilator requirements and the absolute size of the laryngeal aperture [6]. Focus on the remaining opening of the laryngeal inlet seems crucial for further investigations, and may explain why some patients reporting symptoms only have mild laryngeal adduction [11]. We do not have the technical tools to determine the absolute size of the laryngeal inlet, which is an important gap in our knowledge that needs to be filled.

Epiglottis as contributing factor?

A retroflexed epiglottis may disrupt airflow and create turbulence [25], and was found in 28 of 113 EILO patients with simultaneous obstruction at glottic or supraglottic level, and in four of 23 asymptomatic subjects with otherwise normal laryngeal response to exercise [11]. Christensen and colleagues [30] reported on one subject with a peculiar flapping of the epiglottis during exercise, resulting in a staccato-like inspiratory sound, but without subjectively perceived symptoms. Retroflexed epiglottis has also been reported in the context of congenital laryngomalacia [59], and in mechanical insufflation-exsufflation in healthy subjects [60]. Hilland and colleagues [61] did not find epiglottis as a contributing factor when exploring EILO in patients with laryngomalacia in childhood. The contribution of epiglottis in relation to exercise induced inspiratory symptoms remains to be fully established.

Influence of breathing patterns

Fretheim-Kelly and colleagues [62] demonstrated in a study of seven healthy subjects, varying trans-laryngeal pressure patterns during exercise, reflecting that the breathing patterns differ between people with increasing minute ventilation. Some subjects increased tidal volume, whereas others increased breathing frequency. The time ratio of inspiration to expiration also varied, previously reported to be approximately 40:60 [24, 38, 39]. The timing of the breathing patterns may vary, but the volume of air must remain constant. If the resistance increases during inspiration, or the time of inspiration reduces, the flow must increase to get the same volume in. Inspiratory glottic and/or supraglottic dynamic obstruction likely affects work of breathing and respiratory physiology. Walsted and colleagues [63] found increased respiratory neural drive and thus increased ventilation (attributable to greater tidal volume) before observable laryngeal obstruction in six patients with EILO compared to six asymptomatic controls. However, whether patients with EILO adopt a breathing pattern with high tidal volume because they have increased airway resistance or if patients with increased respiratory neural drive is more likely to develop EILO, remains to be determined.

Inspiratory muscle fatigue

Respiratory muscle fatigue is defined as the inability to sustain tension with repeated activity [64, 65], and may develop in healthy individuals during temporary increases in respiratory work, such as strenuous physical exercise [66]. The diaphragm is the primary muscle involved in active inspiration, but other inspiratory muscles may also be implicated by fatigue, such as the intrinsic laryngeal muscles. Fatigue of the posterior cricoarytenoid (PCA) muscle may lead to a smaller laryngeal aperture, as a tired muscle may be less able to resist the increasing negative intraluminal pressures on the laryngeal opening during high airflow rates, and possibly below a critical level for collapse [23, 67].

1.4.2 Suggested causes, or co-morbidities leading to EILO

Both asthma, gastroesophageal reflux syndrome (GERD) [26, 68] and nasal disease [69] have been suggested as causes or contributing factors leading to EILO, with variable scientific evidence. GERD leading to a sensitized larynx has been contradicted by others [70, 71], and treating EILO patients with proton pump inhibitor has not proven effective in reducing symptoms [72]. Activation of pressure- and flow receptors in the supraglottic mucosa may lead to laryngeal hyper-reactivity [23, 73, 74] but evidence lack to support this theory [14]. As EILO and exercise induced bronchoconstriction (EIB) may co-exists [30, 75, 76], it is not unlikely that patients with EILO also reacts to rapid inspiration of cold air by the same mechanisms [43, 77, 78]. Anecdotal reports on worsening of symptoms in EILO during cold and humid air [76, 79] and reports of higher frequencies among athletes participating in outdoor than indoor activities, suggest influence of environmental factors [80]. However, EILO is seen across most sports activities.

The findings of supraglottic collapse in EILO is similar to observations in newborns with congenital laryngomalacia (CLM) [8, 10, 81, 82], thus the (previously) often used labels exercise-induced laryngomalacia and adult-onset laryngomalacia. However, one of the anatomical hallmarks of laryngomalacia, an omega-shaped epiglottis, occurs also in healthy persons [8]. There are no studies to date that indicate that EILO in general can be explained simply by CLM. Plausible modes of inheritance have been suggested [61, 83], but no definite proof of a hereditary component exist.

Psychological factors

Many publications have emphasized a psychological component of EILO [26, 84, 85], primarily based on a small study from the 1990s presenting a link between sexual abuse in early childhood and ILO [86]. However, this has not been substantiated scientifically [16, 79]. To date, overrepresentation of psychiatric disease or personality disorders have not been documented in patients with isolated EILO [16]. High achievers are pointed out as typical EILO patients in numerous publications [16, 26, 87]. However, this may also reflect temperaments in competitive young athletes in general, as well as athletes being more perceptive to minor airflow disturbances during exercise than more sedentary persons [76].

1.4.3 EILO subgroups or “phenotypes”

The ERS/ELS/ACCP Task Force taxonomy established a consensus that laryngeal obstruction can occur at the supraglottic level or the glottic level or a combination of the two, and proposed there were at least two “EILO subgroups”, i.e. glottic and supraglottic EILO [18]. If this represents simultaneous presentation of two different pathophysiological or adaptive processes, or if there is a causal link between the two is not known [88]. This distinction could be of importance as the cause and therapy strategies of these two conditions may differ [1].

Given the complexity of the human larynx and its compound and sometimes conflicting tasks, it seems unlikely that a single factor can explain the entire range of manifestations of EILO [79]. Corresponding heterogeneities regarding exercise induced malfunction should therefore be expected [6]. Further studies are needed to establish the etiology/etiologies for EILO. Until then, development of treatment modalities is still based on targeting symptoms or pathophysiological aspects of the condition.

1.5 Epidemiology

Exercise-induced respiratory complaints are common, reported in 12-14% among college athletes [89] and in 14% among Swedish adolescents [90]. EILO is an increasingly well-recognized cause of exertional dyspnea in the young [91], but key epidemiological data such as prevalence, incidence, age and gender distribution as well as the ratio of exercisers versus top athletes are not fully known in the general population. The material published is influenced by the varying diagnostic criteria employed, and published cohorts may be influenced by referral bias [79].

Occurrence rates of 5% to 7% of the adolescent population have been proposed [30, 32, 80]. A cross-sectional study of adolescents aged 14-24 in Copenhagen tested 98 of the 556 invited subjects with a CLE-test [30]. The tested subjects all reported exercise-related symptoms, and the diagnosis of EILO was set in 42 (43%) of the tested subjects, calculating a minimum prevalence of 7.5%. Other reports found EILO in 12% of active duty military patients with exertional dyspnea [92] and 11% in a suburban pulmonary practice [93].

Patients usually presents with symptoms of EILO in adolescents/young adulthood [79], but it is not known if the condition itself develops during this time-period, or if it is due to increased ventilator requirements occurring at this age due to participation in competitive sports and physical education at school. Most studies report a female predominance [30, 31]; however, not necessarily for prepubertal populations [32].

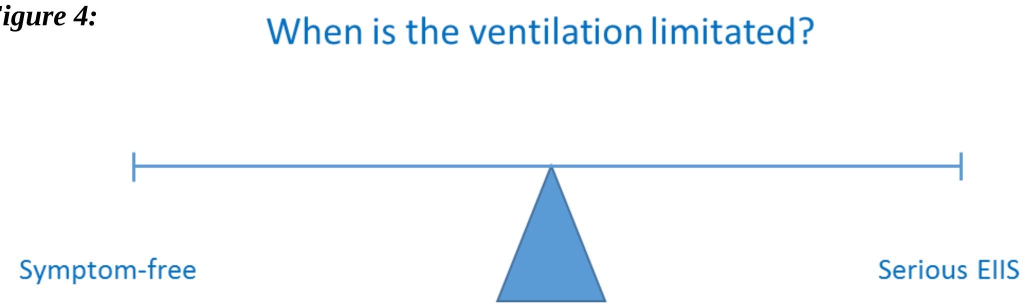
The description of affected patients in the literature range from elite athletes [26, 87] to moderately active children and adolescents affected in normal activity and play [94]. EILO is reported to be frequent in athletes [95], with up to 35% (n=31) of athletes with exertional dyspnea found to have EILO in a retrospective study [31]. However, only athletes with symptoms were investigated and not a random sample of athletes. Rundell and colleagues [80] observed “inspiratory stridor” during an exercise test in 5% of 370 athletes; however, without endoscopic evaluation, leaving the question if some might have passed undetected. A new cross-sectional study from Ersson and colleagues estimated the prevalence of EILO to be 8.1% in adolescent athletes [96].

Based on the current reports, EILO is likely to be relatively frequent in adolescents, and thus there might be a large group of patients with unmet needs who may request treatment for their breathing problem after diagnosis.

1.6 Exercise induced respiratory symptoms and differential diagnosis

Perceived breathlessness during exertion is reported as the most common symptom limiting sporting performance in children and adolescents [97], with the most common cause being poor physical fitness [98]. The sensation of breathlessness/dyspnea is a complex and highly subjective experience [99-101], that likely develops during a continuum as the demand for ventilation exceeds the capacity to provide it [101]. Some adolescents may interpret dyspnea associated with normal physiologic limitation consistent with their abnormal physical fitness level [14, 102]. In a cross-sectional study of Swedish adolescents by Johansson and colleagues, 49% (n=51) of participants reported exercise-induced dyspnea, but had neither exercise induced bronchoconstriction (EIB) nor EILO when tested according to guidelines for these two conditions [32]. There is a need of more normal comparatives in further investigations to establish when exercise induced inspiratory symptoms (EIIS) become abnormal (Figure 4).

Figure 4:



A variety of respiratory problems can limit performance. Structural airway abnormalities, cardiac diseases, primary hyperventilation, poor breathing techniques or psychological causes are possible explanations [103].

Exercise induced asthma (EIA) or exercise induced bronchoconstriction (EIB) is a well described disease, often relevant to young people. EIB is reported to be present in 8-10% of an unselected Norwegian childhood population [104], and in 20–50% of athletes [80, 89, 96, 105, 106]. The pathophysiology of EIB is beyond the scope of this thesis, and therefore not discussed. Evaluating EILO and EIB is challenging and several clinical features may overlap, despite their highly different pathophysiological background.

The main difference of the two conditions is that symptoms in relation to EILO develops when the requirement for ventilation is at its greatest, and usually most evident during the inspiration phase of respiration, and usually disappears 2-3 min after exercise ceases [4]. Patients with EIB on the other hand, can manage well during ongoing exercise, but experience expiratory breathing difficulties and wheeze usually 3-15 min *after* exercise termination [78].

In patients with EILO, respiratory symptoms are often erroneously attributed to poorly controlled asthma, with overmedication and unnecessary medications as a consequence [31, 32, 107, 108]. However, the two conditions may co-exist [30, 75, 76], with reports of 5-10% [30-32] to up to 30-40% comorbidity [4, 76, 109, 110]. The frequent co-morbidity of the two conditions may explain persistence of exercise-related symptoms due to EILO in spite of optimal asthma therapy in some patients [30]. Also, excessive laryngeal closure during exercise, both supraglottic and glottic and both inspiratory and expiratory, has been reported to be apparent in patients with asthma [111, 112]. Thus, laryngeal malfunction might be an integrated part of asthma. Bearing in mind the two conditions when evaluating exercise-induced respiratory complaints seems of importance.

1.7 Symptoms of EILO

Dyspnea during exercise is the most common cited symptom in EILO patients in the clinical literature [17], attributed to the inspiratory phase of the respiratory cycle [6, 14]. However, complaints of dyspnea on expiration have also been reported [109, 113] and patients may be unable to attribute respiratory symptoms to a specific respiratory phase. Other symptoms presented in a sequence of events are throat tightness/chocking sensation, chest tightness, noisy breathing/stridor, hoarseness/voice change and cough [4, 11]. Stridor, a high-pitched musical sound, is produced when turbulent airflow is located in the upper respiratory tracts, and during exercise, often attributed to adduction of the vocal folds, but not necessarily linked to one anatomical structure or causal factor [11]. Relatively similar symptoms of EILO may be interpreted differently by the individual depending on the circumstances and the history of similar sensations [101] and factors relating to personal ambitions and lifestyle [91, 97]. A better understanding of perceived symptoms corresponding to the degree of the laryngeal obstruction is an unmet need in the research field of EILO.

1.8 Diagnostics of EILO

A correct diagnosis of exercise induced respiratory symptoms may be challenging for the clinician [114]. To diagnose EILO, the patient must report exercise induced problems, and the physician must be aware of the condition and know how to confirm the diagnosis.

1.8.1 Symptoms and clinical evaluation

Several questionnaires are now available suited for monitoring and measuring symptoms in EILO [115-118], with good test-retest reliability in quantifying patients' symptoms [118]. However, none have yet been validated as a diagnostic tool [79, 119]. Structured history and detailed symptom description may provide important diagnostic clues, but there is no proven value of structured symptom assessment as per questionnaires in screening for EILO [88]. Self-reported symptoms are often poor predictors of EILO [31, 32, 120]. No specific symptom could be used to differentiate between EILO and EIB in neither an interview-based questionnaire of 150 adolescents [30] nor in a clinical interview of 88 athletes with exertional dyspnea [31].

Similar symptom presentation may arise from the different EILO subgroups, and symptom-based questionnaires cannot easily replace endoscopic evaluation.

1.8.2 Pulmonary diagnostics/surrogate measures

Measurement of airflow to detect upper airway obstruction are described as useful tools in diagnosing EILO. Spirometry with flattened or truncated inspiratory loop [118], eucapnic voluntary hyperventilation [121, 122], bronchial provocation testing with inhaled histamine or methacholine [123, 124], impulse oscillometry and airway perturbation device [125-127] have all been suggested on that matter. To date, both specificity and sensitivity of these measures are either unknown or low [109, 128-130], as well as the reproducibility of inspiratory volume loops. Nevertheless, lung function test at rest may give important information in discrimination from relevant differential diagnoses.

1.8.3 Continuous laryngoscopy exercise-test

The diagnosis of EILO is based on direct visualization of supraglottic and/or glottic narrowing in correlation with characteristic symptoms [79]. Studies from the 1990s reported on flexible laryngoscopy applied in patients before and after exercise [26, 87]. As high airflow quickly decreases after exercise, the obstruction may have resolved before introducing the scope. Thus, the method of introducing the laryngoscope after exercise to diagnose EILO entails a high risk of false negative results. Flexible laryngoscopy *during* exercise on an ergometer bicycle was first described in 1994 [9] and during various body movements in 2000 [52]. The continuous laryngoscopy exercise test (CLE-test) enables visualization of the inciting structures (supraglottic or glottic) and the development of closure, and is now considered gold standard for diagnosing EILO [3]. (Link to web-source explaining the test: https://www.youtube.com/watch?v=N42UevZWKgA).

The CLE-test has been applied in large studies of symptomatic EILO patients and symptom-negative controls [11, 30, 32, 44]. The methodology has been adapted to different exercise modalities such as ergometer bicycling [44], rowing [50] and swimming [120]. Thresholds of exhaustion differs between testing disciplines [131], which may lead to differences regarding inducing symptoms. Therefore, it is beneficial if the laboratory allows patients to perform CLE while performing their specific activity that usually induces their symptoms [50]. The method of CLE requires a comprehensive laboratory set-up and skilled personnel, as well as experience in evaluating the results. Combining ergospirometry with CLE provides valid measurements of the maximal oxygen uptake [94] and may provide important diagnostic clues but is not considered necessary for the diagnosis of EILO.

1.8.4 Evaluation of laryngeal obstruction

Proposed methods for evaluating the severity of obstruction from the laryngeal images obtained from the CLE-test are; image quantification to estimate the laryngeal anterior-posterior diameter or the anterior glottic angle [43, 132], computerized calculations with the "EILOMEA method" [133] and the "CLE-scoring system" (or "Maat score") [1, 134]. The EILOMEA method is based on a rater-selected laryngeal image of the maximum inspiratory obstruction at moderate and at maximum exercise intensity, and requires specially developed soft-ware [133]. More widely used is the CLE-score, based on subjective evaluation by the rater according to a pre-set scheme, evaluating the degree of obstruction from 0 (complete patency) to 3 (almost complete obstruction) at glottic and supraglottic level and at moderate and at maximum intensity (see Figure 7 page 42) [1]. Consistency between the EILOMEA and the CLE-scores have been evaluated and found to be acceptable [134], except for mild glottic obstruction (change from 0 to 1) at maximum exercise possibly being underestimated by the CLE-score compared to the EILOMEA method [46, 134].

The diagnostic cut-off values have been debated for the two methods, emphasizing a need for more material on "normal" laryngeal movements during exercise [135]. Typically a CLE-score ≥ 2 glottic or supraglottic is "diagnostic" for abnormal laryngeal closure [1, 46, 133], and have been applied in several clinical studies [46, 136, 137].

The degree of laryngeal obstruction is reported to correlate well with observed symptom presentation [1], with some outliers; i.e., young athletes who continue to run despite severe symptoms of distress and relatively extensive laryngeal obstruction, while others stop early with seemingly minor symptoms and an open larynx. Today we cannot predict in any way exactly at what degree of narrowing the breathing of any given person is subjectively hampered (Figure 4). Thus empirically defined CLE-score cut-off values are not necessarily adequate in a clinical setting, emphasizing the importance of evaluating also the patients' subjective experience in relation to the objective clinical findings [46].

1.9 Treatment modalities in EILO

The optimal approach for treating EILO remains to be determined as the published evidence-base on EILO treatment is heavily influenced by anecdotal reports and retrospective reviews, with small sample sizes and unclear outcome measures [17, 138]. Most reports are solely based on subjective reporting of symptoms before and after an intervention. Only a few have used visualization of the laryngeal response as an outcome measure. There are currently no published randomized controlled treatment trials, and treatment of EILO has been said to represent an "evidence free zone" [118]. See treatment overview in Appendix 1.

The common goal for treatment measures is to relieve the perception of exercise induced respiratory symptoms. Some of the modalities that have been applied in an attempt to relieve symptoms during exercise are; psychotherapy [139], speech therapy [140-143], inhaled ipratropium bromide [144], different forms of biofeedback techniques [145, 146], inspiratory muscle training [147-151] and laser supraglottoplasty [152-155].

The heterogeneity of findings when investigating EILO patients [11] indicate that better subgrouping of EILO may facilitate individually tailored treatment, and increase success rates for different treatment modalities [79]. Benefits from a multidisciplinary team (MDT)-approach for treating EILO has also been highlighted [136, 156]. Further development of treatment options and proper evaluation of the response patterns after interventions are needed.

1.9.1 Information and biofeedback

Figure 5: *Visualization of laryngeal responses on the monitor, i.e. biofeedback*

The first aim of treating EILO is educating the patient about the diagnosis, the prevalence, its trigger factors and reassurance to the patient/and caregivers that the condition is not life-threatening [6, 141, 157], despite the fact that symptom presentation can sometimes seem so. A multidisciplinary approach on a single visit with visual biofeedback of laryngeal responses, patient education, breathing exercises and relaxation techniques from speech therapy is reported to reduce symptoms and maintain or increase the activity level of patients, regardless of EILO subgroup [146]. Simply observing their own malfunctioning larynx has been reported to help in most patients with mild or moderate disease [141, 145] (Figure 5). The structured information and breathing advice given to all patients at our institution has been named IBA; information and breathing advice. However, these techniques take time to learn [158] and they require practice to apply the techniques during high intensity exercise. Olin and colleges [145] reported on the first systematic use of therapeutic laryngoscopy during exercise (TLE) in an uncontrolled study. Three quarters of the participants (total n= 64) reported subjective effectiveness of the technique [145, 159]. The Olin Exercise induced laryngeal obstruction Biphasic inspiration (EILOBI)-breathing techniques is based on a principle that sudden changes in airflow during inhalation seem to positively affect inspiratory laryngeal configuration [145, 159, 160]. The “Hull-Hoover technique” is another described technique that encourages athletes to work around creating audible sounds replicating the word “hoover” to modulate airflow both on inspiration and expiration [158]. A recent study evaluating specialized physiotherapy targeting breathing pattern, in combination with elements of cognitive behavioural therapy, reported improved subjective respiratory symptoms and reduced laryngeal obstruction during CLE-test in four athletes with EILO [161]. Overall, the findings of the different techniques are preliminary and suggest a reasonable rationale for proceeding to better planned studies as they also can be applied during high-intensity training.

Efficient breathing patterns during exercise can to a certain extent be trained [141], but may not be sufficient for a top athlete that must increase both tidal volume and breathing frequency to improve ventilation at maximum exercise intensity.

1.9.2 Speech therapy/Laryngeal control therapy (LCT)

Speech therapy is reported as the mainstay of conservative treatment in EILO patients [140, 141, 146], with 75-80% of patients reporting subjective improvement in uncontrolled studies [141]. Various breathing techniques guided by a speech language therapist (with or without laryngoscopy) is applied to gain respiratory control and self-awareness of sensations of laryngeal tension [141, 157, 162]. The techniques may require adjustment for application during exercise, and athletes are encouraged to practice techniques daily [141, 157].

A systematic review on speech-therapy in ILO, not differentiating the inducer of symptoms, found that the evidence for its use is in its infancy with the majority of studies being in the exploratory stage of research [143]. Speech therapy remains to be validated by well-controlled treatment trials in patients with EILO using standardized outcome measures [146]. When need for multiple sessions, this “one-to-one” treatment by a speech therapist may be perceived as resource-demanding in a country with long travel distances, such as Norway.

1.9.3 Inspiratory muscle training

Inspiratory muscle training in general

Inspiratory muscle training (IMT) is a form of respiratory muscle training (RMT) and is based on a course of breathing exercises with resistance during inspiration, loading the inspiratory muscles during the training session. IMT aim to strengthen the inspiratory muscles and increase the endurance [163, 164], and is usually split into two training modalities (Table 1):

Table 1: *Training modalities of inspiratory muscle training (IMT)*

	Inspiratory muscle STRENGTH training (IMST)	**Inspiratory muscle ENDURANCE training (IMET)**
Intensity and force	HIGH	LOW
Velocity of muscle contractions	LOW	HIGH
Duration of stimulus	SHORT	LONG

The respiratory muscles are morphologically and functionally similar to skeletal muscles and can be trained both for strength and endurance [163]. IMT have been used in both healthy and in patients with respiratory system impairment to strengthen the diaphragm and other respiratory muscles to enhance breathing efficacy [49]. Conflicting results on the effectiveness from IMT on improvement of sports performance in general in healthy subjects have been reported [165, 166]. The putative mechanisms to explain improved exercise performance from IMT include; decreased perceived breathlessness, strengthening the respiratory muscles and hence minimizing respiratory fatigue, and reducing the metaboreflex phenomenon [65, 165]. In response to inspiratory muscle fatigue and dyspnea, the metaboreflex may redistribute blood flow to the respiratory muscles while decreasing blood flow to the activated peripheral musculature. However, the literature appears inconclusive on the field of IMT and exercise performance enhancement [167], and appears beyond the scope of this thesis.

In general, muscular strength increases as a result of adaptive changes and altered neural drive during the first weeks of training [168]. Chronic training increases the passive stiffness of locomotor muscles and thereby increase the intrinsic stiffness, which may reduce a tendency for upper airway collapse [169, 170].

There are several IMT-devices available on the commercial market using different principles of resistance (Table 2), which can be controlled by factors such as time, intensity and/or frequency of training. There are no evidence based guidelines for which modality or how to build training programs for different clinical situations [49].

Table 2: *Types of inspiratory resistance applied in inspiratory muscle training (IMT)*

Types of inspiratory resistance applied:	Inspiratory muscle strength training (IMST)	Inspiratory muscle endurance training (IMET)
Pressure threshold loading	X	X
Flow-resistive loading	X	X
Voluntary isocapnic hyperpnea		X

Inspiratory muscle training and EILO

IMT is suggested as treatment for EILO because of the PCA/diaphragm-relationship [37]; facilitating enhanced diaphragmatic strength will also lead to enhanced laryngeal abduction. This was first described clinically in a case report from Archer and colleagues [171], using an improvised inspiratory muscle trainer made of anaesthetic equipment that improved the patient's symptoms when used during symptoms of ILO at rest.

Application of a training stimulus as IMT in EILO will possibly lead to:

1) Facilitation of a more effective and better controlled laryngeal abduction due to a better controlled or a stronger PCA/diaphragm-relationship [45], leading to delay (or prohibition) of airway obstruction.

2) Less tendency for upper airway collapse due to increased active (neural) tone and passive (intrinsic) stiffness of the dilators, or both [169].

3) Increased inspiratory muscle strength including intrinsic laryngeal muscles, leading to generation of a smaller fraction of maximal force in the respiratory muscles with each breath and thereby decreasing the sense of effort [148].

At the laryngeal level, the degree of load-dependent abductor activity appears to vary directly with ventilator resistance [23], and resistive loading during inspiration have been found to increase the inspiratory activity of laryngeal abductors in anesthetized animals [24]. To what extent application of IMT facilitates the desired response of a larger laryngeal opening had so far not been proven in studies.

Table 3: *Publications of IMT in EILO*

Authors, year	Case(s)	IMT intervention	Outcome
Ruddy et al, 2004	A 15-year-old male rower	Pressure threshold loading for 6 weeks and one session behavioural therapy/week	Pi_{max}, subjective scoring of dyspnea and exercise testing
Mathers-Schmidt et al, 2005	A 18-year-old female soccer player	Pressure threshold loading 5 weeks on-off (total 16 weeks) and one session behavioural therapy	Pi_{max}, subjective scoring of dyspnea, exercise testing and laryngoscopy *after* exercise
Dickinson et al, 2007	A 25-year-old athlete	Pressure threshold loading for 11 weeks	Pi_{max}, subjective scoring of dyspnea and exercise testing
Clemm et al, 2018	A 18-year-old male athlete and a 20-year-old female athlete	Flow-resistive loading for 6 weeks and one session with IBA	Subjective scoring of dyspnea and CLE-test
*Gaylord et al, 2020	Five athletes aged 10-16, (one male, four females)	Pressure threshold loading for 5 weeks	Subjective scoring, maximum phonation time and duration of running.
Total	**10**		

IMT: Inspiratory muscle training; Pi_{max}: Maximal inspiratory mouth pressure; CLE-test: continuous laryngoscopy exercise-test; IBA: information and breathing advice with biofeedback.

** published after paper #II of this thesis*

Studies proving that IMT affects EILO are scarce. To the best of our knowledge, only ten cases of IMT used to treat EILO patients have been published, evaluating both threshold training and resistive load training (Table 3). Eight cases reported subjective effect, one unchanged and one reported worsening [147-150, 172]. The studies are hard to compare due to variabilities between the participants, the device and protocol applied and the use of different outcome measures.

1.9.4 Pharmacological therapies

Several pharmacological agents have been used to decrease the impact from triggers of ILO [173], but as with reports of other managements many of the studies do not differentiate among patients with symptoms at rest or induced by exercise. Inhaled anticholinergics before exercising are reported to reduce symptoms in EILO, explained by reducing the sensory mediated laryngeal closure [144, 174]. Also, heliox, a combination gas of helium and oxygen [175, 176], botulinum toxin injection [156] and proton pump inhibitor (PPI) [72, 177] have been suggested, all of which currently lack support of evidence.

1.9.5 Supraglottoplasty

The method of endoscopic supraglottoplasty was first described in patients with supraglottic obstruction and “adult laryngomalacia” in 1995 by Smith and colleagues [81]. The aim of the procedure is to reduce the possibility of supraglottic collapse, and to increase the structural integrity of the supraglottic structures. The procedure was based on the surgical technique used to treat congenital laryngomalacia. Subsequently, different surgical techniques such as cold steel and laser for supraglottoplasty have been applied.

Initially published case reports demonstrating effect from supraglottoplasty in supraglottic EILO [8, 10, 41, 54, 59, 178-180] have in recent years been followed by larger series of patients [137, 152-155] (Table 4).

Table 4 *Reports of supraglottoplasty in exercise-induced laryngeal obstruction*

Authors, Year	**Cases**	**Examination before surgery**	**Examination after surgery**
Smith et al, 1995	1	Exercise and laryngoscopy	CLE-test
Bent et al, 1996	2	Exercise and laryngoscopy	CLE-test in one
Björnsdottir et al, 2000	2	CLE-test	CLE-test
Chemery et al, 2002	1	Laryngoscopy after exercise	Laryngoscopy after exercise
Mandel et al, 2003	1	Laryngoscopy and spirometry	Laryngoscopy and spirometry
Richter et al, 2008	3	CLE-test	CLE-test
McNally et al, 2010	1	Laryngoscopy post exercise	Symptoms and laryngoscopy after exercise
Maat et al, 2011	23	CLE-test	CLE-test in 19
Dion et al, 2012	3	Exercise flexible laryngoscopy	Exercise flexible laryngoscopy
Orbelo et al, 2014	1	Exercise flexible laryngoscopy	Exercise flexible laryngoscopy
Norlander et al, 2015	14	CLE-test	Symptoms
Mehlum et al, 2016	17	CLE-test	Symptoms in 15 and CLE-test in 11
*Famokunwa et al, 2020	19	CLE-test	Symptoms and CLE-test in 14
Total	**88** [a)]		

Studies published in English (or abstract in English) were identified from search in PubMed
CLE-test: Continuous laryngoscopy exercise-test
** published after paper #III of this thesis*
[a)] *Sandnes et al, 2019 (Study #III of present thesis),n=45 evaluated with symptoms and CLE-test before and after in all*

All studies indicate that surgery has a beneficial impact on EILO-related symptoms, and the literature suggest that the procedure is safe, based on descriptions of surgical treatment of 69 cases worldwide prior to 2018 [181, 182]. The published data may be confounded by selection bias due to lack of a randomized approach to patient selection with only highly motivated patients included, and only a few studies used laryngoscopy during exercise to rate the success postoperatively [152, 154].

To the best of our knowledge, no serious complications after supraglottoplasty on EILO patients have been reported to date. No studies have evaluated the optimal surgical technique, and in fact, many of the published studies do not specify the technique applied. Only the study by Maat and colleagues evaluates long-term effect of surgery using laryngoscopy [152].

1.10 Follow-up of EILO after treatment

The natural course of EILO is unknown. To the best of our knowledge, only three studies have investigated long-term symptoms in patients with EILO [144, 152, 155], and there are currently no studies with information covering more than five years of follow-up after diagnosis. Experience from congenital laryngomalacia suggest that laryngeal abnormalities originating at a young age may resolve naturally with growth and maturation [183, 184]. This scenario has led some researchers to postulate that growth of the larynx would naturally reduce/resolve EILO in adolescents. Thus, they hypothesize that young patients with EILO "will grow out of the problem" through maturation and growth of the larynx [29].

In a study of 17 EILO patients [144], where six initially were treated with inhaled ipratriopium bromid before exercise, 16 reported spontaneous resolution of symptoms at a median time of 5 months after diagnosis (variability from 1 week to 5 years). One still used inhalation treatment before exercise at follow-up. However, 6 of the patients had quit their competitive sports activity which was the original trigger of their symptoms.

A retrospective study of 19 surgically and 14 conservatively treated EILO patients re-examined 2-5 years after (and age > 20) [152] found reduced self-reported symptoms and improvement of laryngeal obstruction during exercise (evaluated by CLE-test) with normalization in 16/19 treated with supraglottoplasty compared to 3/14 of the conservatively treated. Similar findings were presented in a symptom-based follow up study 1-3 years after a diagnostic CLE-test. By comparing, surgically treated versus conservatively treated, they found subjective improvements of symptoms only in the surgically treated group [155]. In both studies, the activity level was also reduced, so we do not really know if symptoms had declined *per se* or if symptoms were less bothersome due to less exposure to the trigger.

The few published follow-up studies of EILO collectively suggest that laryngeal obstruction does not improve with age, whereas symptoms might improve, possibly due to reduced physical activity and/or changes of exercise habits.

1.10.1 The EILO-register

In our hospital around 200 CLE-tests are conducted annually. Aiming to collect information about the EILO patient population, their laryngeal response patterns, evaluation after treatment interventions and to observe how the condition generally progresses. The *EILO-register* was created in January 2013 (REK 2016/1898). Inclusion is consent-based with a good overall cover ratio, only one patient has declined to be registered so far. The register data are obtained from the patient and the clinician and stored unidentified. Variables of interest are age, gender, self-reported debut of respiratory symptoms, previous diagnoses, use of asthma medication, type and level of sports, hours of physical activity per week, exercise symptoms and their influence on daily life. Data are obtained from an established questionnaire, the CLE recordings with scores, and the ergospirometry data. The treatment choice and further referrals for comorbidities are noted by the clinician.

2. State of the art

Exercise as an inducer of laryngeal obstruction was reported over two decades ago, but our understanding of the disease entity is still rudimentary. There are still unanswered questions about the etiology, prevalence, effects of treatment, prognosis and natural course of EILO. Still, some improvements have been made the last years. One important milestone was the establishment of endoscopy performed during ongoing exercise as gold standard for making an EILO diagnosis. A setup for continuous laryngoscopy during exercise [3] is now widely used. This was important for the taxonomy established by the "ERS/ELS/ACCP Task Force" group in 2013, settling EILO as the overall term for airflow obstruction at the laryngeal level during high intensity physical exertion [13]. The term has been fully adopted in Europe, whereas the condition is still known predominantly as VCD in Australia, and in the United States as paradoxical vocal fold motion (PVFM) [136].

The "semi-objective" classification of EILO severity by CLE-score most employed, still represents a rather crude approach. Subjective perception of exercise symptoms does not always match CLE-score findings. Outcome tools to quantify the subjective impact of EILO or evaluation after treatment are currently an important unmet need in this research field.

Different treatment modalities offered varies between centers but are in general based on empirical data and lack high-quality evidence. Development of robust treatment modalities seems important from a health care perspective, as the debut age of EILO is also a vulnerable age for decline in sporting activities. Preliminary findings in treatment studies warrant further investigations. At our institution during this study, first-line therapy for EILO (received by all patients) was information about the condition and physician-guided structured breathing advice while patients were observing their laryngeal responses on the monitor (biofeedback), hereafter referred to as IBA. Second-line treatment options were physician-guided IMT or speech therapy, offered to patients based on the degree of laryngeal obstruction, perceived symptom severity, patient motivation, and the availability of the apparatus/speech language pathologist. Supraglottoplasty was reserved for highly selected supraglottic cases. Proper long-term follow-up of conservatively and surgically treated EILO is needed. The EILO register at Haukeland University Hospital is (and will be) an important tool in the process of collecting more data on EILO and to perform long-term follow-up.

3. Aims of the thesis

The overall aim of this study was to explore short- and long-term influence on laryngeal obstruction and subjective symptoms in EILO patients treated with inspiratory muscle training or laser supraglottoplasty.

3.1 Specific aims of the studies

Study #I: To investigate laryngeal response pattern(s) during inspiratory muscle training (IMT) in healthy subjects using laryngoscopic evaluation and imaging.

> **Research question #1**: Can laryngoscopy confirm the relationship between the diaphragm and the posterior cricoarytenoid (PCA)-muscle by visualizing laryngeal abduction in healthy subjects?
>
> **Research question #2:** Does inspiratory muscle strength training (IMST) influence the size of the inspiratory laryngeal aperture in healthy subjects?
>
> **Research question #3:** Does inspiratory muscle endurance training (IMET) influence the size of the inspiratory laryngeal aperture in healthy subjects?

Study #II: To expand our knowledge and to explore possible effects from inspiratory muscle training in patients diagnosed with EILO.

> **Research question #4**: Does six-weeks of IMT influence self-reported exercise induced respiratory symptoms in patients with EILO?
>
> **Research question #5:** Does six-weeks of IMT influence the laryngeal obstruction (evaluated by CLE-score) during exercise in patients with EILO?

Study #III: To investigate the efficacy and safety of laser supraglottoplasty for patients with supraglottic EILO, with CLE-tests performed before and after surgery.

> **Research question #6:** Is laser supraglottoplasty a safe treatment for patients with supraglottic EILO?

Research question #7: Does supraglottoplasty influence self-reported exercise induced respiratory symptoms in patients with supraglottic EILO?

Research question #8: Does supraglottoplasty influence the laryngeal closure (evaluated by CLE-score) in patients with supraglottic EILO?

Study #IV: To assess changes of self-reported symptoms and laryngeal outcomes in EILO shortly after treatment with standardized information and breathing advice (IBA) plus IMT. After 4-6 years, comparing self-reported symptoms in the same individuals with a control group with EILO who had only received IBA.

Research question #9: Does self-reported exercise symptoms and laryngeal outcomes in EILO change shortly after IBA plus IMT?

Research question #10: Does self-reported exercise symptoms after 4-6 years differ between EILO patients who only received IBA compared to EILO patients who additionally received IMT?

4. Material and Methods

4.1 Participants

The thesis was based on two groups of participants (Table 5); healthy medical students from the Medical Faculty in University of Bergen and patients diagnosed with EILO at the outpatient clinic, a cross-professional collaboration between Department of Paediatrics and Otolaryngology at Haukeland University Hospital Bergen, Norway.

Table 5: *Overview of the study participants and inclusion*

	Study participants	Inclusion
Study #I	20 asymptomatic students	Recruited from the University of Bergen
Study #II	28 athletes with EILO	Consecutively recruited from the outpatient clinic 2012-2014, depending on availability of IMT-device
Study #III	45 patients with EILO	Retrospectively identified from the *EILO-register* based on receiving Supraglottoplasty during 2013-2015
Study #IV	55 patients with EILO	Retrospectively identified from the *EILO-register* based on receiving six-weeks of IMT and/or IBA during 2013-2015

EILO: Exercise induced laryngeal obstruction; IMT: Inspiratory muscle training; IBA: Information and breathing advice (with biofeedback)

4.1.1 Exclusion criteria

Prior to inclusion, all participants were screened for the following exclusion criteria: self-reported hypersensitivity to Xylocain® (local anaesthetic used during laryngoscopy) and additional lung disease or EIB as explanation for the patient’s symptoms. Exclusion criteria for healthy volunteers in Study #I was self-reported history of exercise-related breathing problem. Data from the patients that declined to participate in the studies were excluded. In Study #II and #III, patients were excluded due to; insufficient data either pre-test or post-test, or characteristics of laryngomalacia at rest.

4.2 Study design

The four studies were conducted within an explorative approach in a field of medicine not previously studied in larger patient groups with objective methods. The design was combined descriptive and quasi-experimental observational.

Study #I (Paper #I)	A cross-sectional study of healthy volunteers.
Study #II (Paper #II)	A prospective pre-post study of EILO patients
Study #III (Paper #III)	A retrospective pre-post study of EILO patients identified from the *EILO-register*.
Study #IV (Paper #IV)	A follow-up study of a cohort of conservatively treated EILO patients retrospectively identified from the *EILO-register*.

4.3 Ethics

All studies were approved by the Regional Ethics Committee (REK number 2009/2111, 2011/784 and 2016/1898). Informed written consent was obtained from all participating subjects and/or their guardian/parent before inclusion in their respective studies or inclusion in the EILO-register. The participants could withdraw their consent at any time. The ethical considerations when planning and under conduction of the included studies were based on the Declaration of Helsinki [185] and the Norwegian Health Research Act [186].

4.4 Sample size

Explorative studies do not have *a priori* hypotheses (to be tested), but subsidiary hypotheses (to be explored), thus calculation of sample size and final number of patients that should be included is difficult [187, 188]. One of the main outcomes in the studies (the CLE-scores) is relatively new and essential information is insufficient, we especially lack information on the distribution, both in patient groups and in healthy. However, previous attempts to calculate power before a study on evaluating congenital laryngomalacia compared to healthy controls in our group [61], has formed the basis of power assumptions in our studies. Based on “in-house” experience, we assume that mean CLE sum-score in this patient group is approximately 4 and that one standard deviation (SD) would account for approximately 10% (0.5) of this mean. The values are based on the scoring system published by Maat and colleagues [1]. Thus, 95% of the patients (2SD) would have a total score of about 3 to 5. If the intervention leads to a change at group level less than 0.5, it is likely to be of little clinical benefit and the intervention will probably be of little value. Therefore, we have considered it reasonable to set a lower detection limit to 1 SD (0.5), the significance-level (alfa) to 0.05 and beta to 0.2.

Given this scenario, to detect a difference in CLE sum-score of 0.5 point after an intervention using a two-tailed test with an alpha value of 5% and a power of 80%, 16 subjects had to be included.

4.5 Study procedures

To evaluate changes possibly caused by the treatment, several methods were used to capture both laryngeal opening, self-reported symptoms and cardiopulmonary data (Table 6).

Table 6: *Overview of examinations used in Studies #I to #IV*

	Study #I	**Study #II**	**Study #III**	**Study #IV**
Spirometry at first visit	X	X	X	X
Questionnaire				
- At time of diagnosis		X	X	X
- At time of evaluation after treatment		X	X	X
- At follow-up 4-6 years after diagnosis				X
Video-recorded trans-nasal fiberoptic laryngoscopy:				
- At rest with IMT training program	X			
- During continuous exercise test (CLE-test)		X	X	X*
Evaluation of laryngeal responses/obstruction				
- Modified scoring system	X			
- CLE-score by Maat and colleagues		X	X	X*

CLE-test: Continuous laryngoscopy exercise-test, CLE-score: grade of laryngeal obstruction by Maat et al [1]
* The CLE-test are from time of diagnosis and "shortly after IMT" in Study #IV

4.5.1 Examinations pre-post

Questionnaire

A questionnaire used in our clinic for several years served to obtain the medical history, perceived symptoms, activity level of the patient and the influence of their exercise related symptoms on daily life activities (Study #II, #III, #IV). Answers were based on an ordinal scale served to grade the severity of symptoms and respiratory complaints during physical exertion. All participants (and/or their guardian) completed this at every visit, i.e., before and after treatment. A follow-up questionnaire and a consent form were sent home to all eligible patients in Study #IV (Appendix 3).

Exercise test and lung function measurements

Spirometry was performed in all subjects with a Vmax 22 © spirometer (*SensorMedics, Yorba Linda, CA, USA*) according to guidelines [189].

A trans-nasal flexible fiberoptic laryngoscope (Olympus ENF-P3©, Tokyo, Japan), diameter 3.5 mm, introduced after applying a decongestive nasal spray (Rhinox©) and local anesthesia (Xylocaine©), was secured using a custom designed helmet in a position allowing for a good view of supraglottic structures and the vocal folds in all participants.

In Study #I continuous video-recorded laryngoscopy was performed at rest during the IMT maneuver. In Study #II, #III and #IV, the CLE-test was applied to set the diagnosis of EILO and to evaluate treatment. Continuous video-recorded laryngoscopy was performed throughout a maximal cardiopulmonary exercise test on a treadmill *(Woodway ELG 70, Weil am Rhein, Germany)* using a computerized and modified Bruce protocol, increasing speed and/or elevation every-one minute, aiming to reach maximum exercise capacity after 6-14 minutes [190]. The set-up was coupled with integrated video-recording of the upper part of the body and sound-recordings was performed, as previously described [3] (Figure 6).

Figure 6: *Set up for continuous laryngoscopy exercise-test (CLE-test), as described by Heimdal et al [3].*

The test was considered successful if the patient continued until exhaustion or was stopped by respiratory distress, preferably supported by a plateau in oxygen consumption and/or the heart rate response. Maximum voluntary ventilation (MVV) and ergospirometry data were collected in conjunction with the CLE-test using a Jaeger Oxycon Pro Cardiopulmonary Exercise testing system (Viasys Health Care, Yorba Linda, CA, USA).

Evaluation of laryngeal obstruction

To evaluate the degree of obstruction in the larynx, video-recordings of the larynx was assessed retrospectively and in a random order by experienced raters.

In Study #I the laryngeal movements were scored by an experienced otolaryngologist (J-HH) using a pre-set system, modified from Maat and colleagues [1] as all recordings were obtained at rest. Laryngeal movements were graded supraglottic and glottic from: maximal abduction (+2), moderate abduction (+1), neutral position (0), moderate adduction (−1), and severe adduction (−2). Laryngeal adduction has been reported to be a normal phenomenon at end-inspiration [191]. Therefore, the inspiration was separated into three phases, the initial-, mid, and end-inspiration, and only observations from the initial- and mid-inspiratory phases were tabulated.

In Study #II, #III and #IV the scoring system of laryngeal movements previously described [1] was applied according to a pre-set scheme (Figure 7). Scores were assigned at moderate (i.e. when the test person changed from walking to running) and at maximal exercise intensity at glottic (labelled A and C, respectively) and supraglottic (labelled B and D, respectively) levels, and additionally a total sum-score labelled E. The diagnosis of EILO was set when the patient's symptoms coincided with laryngeal obstruction graded as 2 or more, either at the supraglottic level or glottic level [11, 135].

The video-recordings were presented in random order to two experienced raters (HHC and ODR) in Study #II and #IV, and in pairs (pre-post) to four experienced raters (HHC, ODR, MH and JHH) in Study #III. A blinded procedure was tested in Study #III but proved impossible, as the surgical changes were impossible to hide. Thus, assessments were open and consensus-based, and disagreements were solved by consensus. Clinical symptoms during the CLE test were recorded in a questionnaire by the physician performing the test.

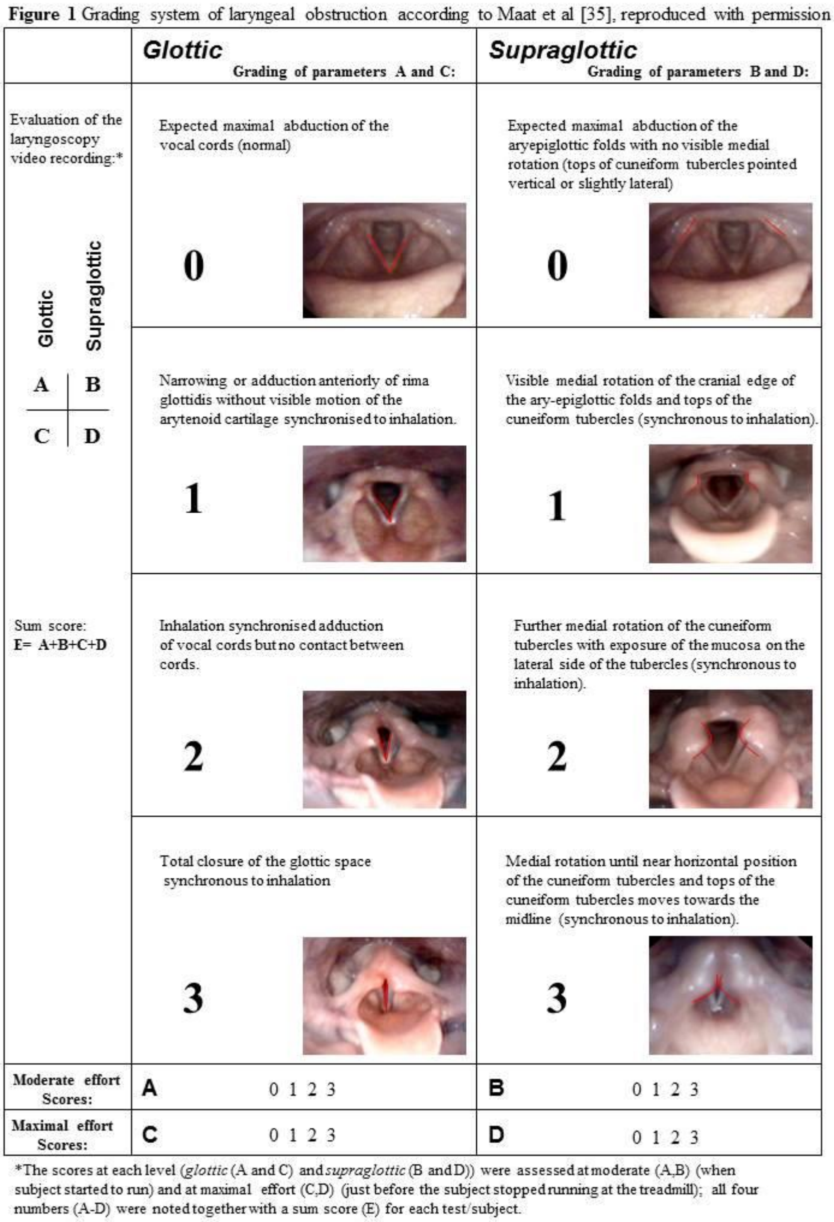


Figure 7: *Grading system of laryngeal obstruction according to Maat et al [1], reprinted with permission from European Archives of Oto-Rhino-Laryngology*

4.5.2 Treatment modalities

Information/biofeedback

All patients (and their guardian if present) received information about the diagnosis, its benign nature and physician-guided breathing advice (IBA), while observing their laryngeal responses on the monitor (biofeedback) at time of their first visit. (Link to web-source https://www.youtube.com/watch?v=jaS0qZN4X9c). The advice consisted of guidance in posture, diaphragmatic breathing, and relaxation of the shoulder girdle while illustrating the laryngeal response on the monitor. Advice was given to avoid noisy breathing/stridor when exercising, to recognize the first signs of breathing problems and to gain control of the breathing when these signs arise. All adolescents were encouraged to maintain their desired level of physical exercise, and to practice on the breathing advice given during their first visit while exercising.

Inspiratory muscle training

Because of availability of the apparatus and the possibility of two modes of resistance (strength and endurance), we used the apparatus Respifit S© (Biegler GmbH, Mauerbach, Austria), a flow-resistive loading device, in Study #I, #II and #IV (Figure 8).

Figure 8*: Inspiratory muscle training with a resistive loading device (Respifit S©)*

The same apparatus was used to measure the maximal inspiratory mouth pressure (Pi_{max}), using the best value of ten according to guidelines [192] in order to set correct resistance.

To promote correct breathing technique during the maneuver, the participants were seated with a nose clip and instructed at the first session to inhale using the diaphragm and expanding the thorax, and to minimize movements of the shoulders in cranial direction.

In Study #I we tested two modes of inspiratory muscle training in accordance with the manual provided by the manufacturer, i.e.:

A) Inspiratory muscle strength training (IMST) with the resistance set to produce mouth pressures ≥ 80% of Pi_{max}

B) Moderate resistance or inspiratory muscle endurance training (IMET) with the resistance set at 60-80% of Pi_{max}.

In the IMST sessions, subjects performed five maximal inhalations repeated three times, separated by a one-minute break. The participants were instructed to exhale passively to residual volume (RV), and then inhale from residual volume to total lung capacity (TLC), utilizing an appropriate breathing pattern with maximal effort, i.e. a rapid and complete inhalation. In the IMET sessions, subjects performed repeated breath cycles with the mouthpiece in place, inhaling and exhaling to near RV and TLC using diaphragmatic breathing at a rate of 12-16 times per minute for one minute. This was repeated three times with 30 seconds breaks in between.

The frequency and power were guided by an animation program ensuring correct use of the device, and data from each training session were stored on a memory-card for measurement of compliance with the treatment.

In Study #II, the same modes of training were instructed, and resistance set after measurement of Pi_{max}, and the participants borrowed the apparatus home. They were instructed to train every day, in cycles of two days with IMET followed by one day of IMST, for a total of six weeks. The same treatment protocol was applied in patients receiving IMT in Study #IV at time of diagnosis.

Supraglottoplasty

All operated patients in Study #III had been informed about the surgical procedure and of risk factors. Surgery was performed in general anaesthesia with suspension micro-laryngoscopy and endoscopic supraglottoplasty with carbon dioxide laser, as previously described [153]. The procedure had been performed by one of two surgeons. The oral laser endotracheal (LET) tube was positioned posteriorly, protecting the interarytenoid area. A Lindholm/Benjamin laryngoscope was introduced into the vallecular exposing both aryepiglottic folds and epiglottis. The arytenoid was grasped with micro laryngeal forceps and pulled slightly forward and medially stretching the aryepiglottic fold, revealing the amount of abundant arytenoid tissue. Laser beams of 2-4 watt focused with micro spot was utilized. The aryepiglottic fold was split anteriorly down to the level of the musculus aryepiglotticus approaching the cranial margin of plica ventricularis. Then tissue around the top of the cuneiform cartilages was removed in a circular pattern, creating a triangular shaped excision (Figure 9).

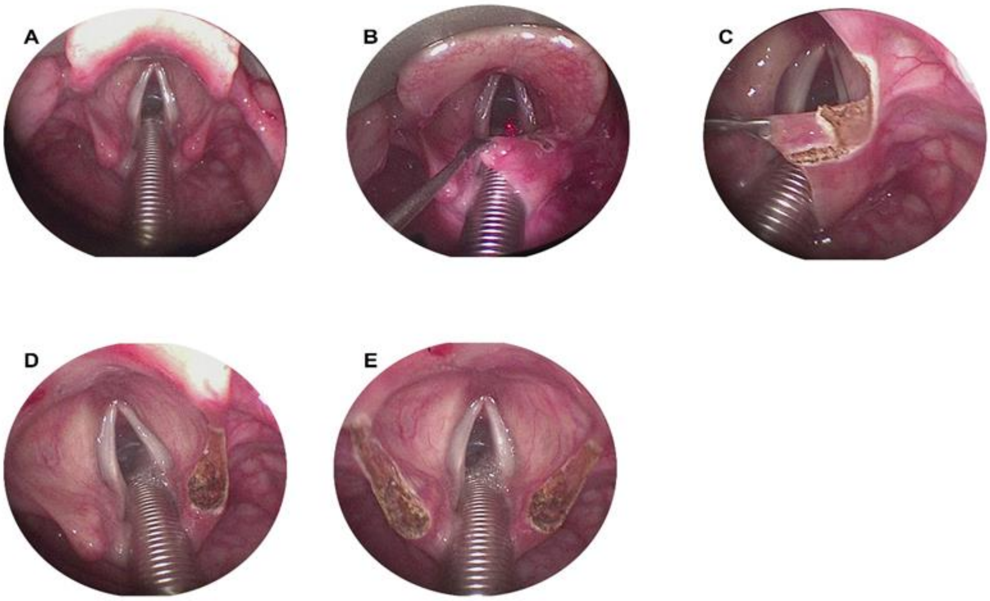


Figure 9*: Stepwise description of supraglottoplasty with CO2-laser in EILO patients. A: Intubation in trachea, B-C: Cartilages moved medially with micro forceps. Aryepiglottic folds divided along the lateral edge of epiglottis. D: The cuneiform and corniculate cartilages are removed with laser. E: the procedure performed both sides*

In cases where the cuneiform tubercles were pointy and exposed in the excision, parts of this cartilage were included in the resection. The same procedure was performed bilaterally making sure to avoid endothelial damage to the interarytenoid covered by the LET-tube. In some cases, with epiglottic involvement, epiglottotomy and rotation of the epiglottis toward the tongue base (epiglottopexy) was also performed. Specific anatomic decisions were guided by findings on preoperative video-recording during CLE-test and surgery tailored to the individual patient's anatomy [153, 181].

4.6 Statistical analysis

The statistical analysis in Study #I to #IV are presented in Table 7 and statistical reporting was according to SAMPL guidelines [193]. Main outcomes were perceived subjective symptoms (obtained by questionnaires) and laryngeal obstruction (CLE-scores or modified scores in Study #I). The data were reported as means with 95% confidence intervals (CI) or ranges for continuous normally distributed data and counts with percentages of group-total for categorical data, as appropriate. The CLE-scores are by nature ordinal and categorical, ranging from 0-3. Due to the few number of categories, data were calculated and reported as mean, as this is considered to provide more information than medians and interquartile ranges [194]. Missing values were not included in the analyses, the total number included in all analysis were stated. The laryngeal scores were tabulated in full in Study #I, a descriptive study presented with counts and percentages. In Study #II to #IV, group comparisons were performed with Student's t-test or one-way analysis of variance (ANOVA) for normally distributed and Mann-Whitney U test for non-normally distributed, categorical, and continuous variables, as appropriate. The distribution of continuous variables was assessed by descriptive statistics and histograms, and parametric tests were applied after accounting for normal distribution. Sufficient number of observations in the studies justify use of parametric significance tests according to the central limit theorem [195]. To account for multiple correlated measurements in the same test subject in Study #II and #III, mixed linear regression with fixed effects including three- and two-way interactions was applied.

Only two-sided tests were used and p-values below 0.05 were considered statistically significant. All analyses were performed with SPSS version 24 (SPSS, Chicago, IL, USA).

Table 7*. Statistical methods used in Study #I to #IV.*

Statistical methods	***Study #I***	***Study #II***	***Study #III***	***Study #IV***
Group counts and frequencies	x	x	x	x
Mean and 95% confidence intervals		x	x	x
Student's t-test		x	x	x
Mixed linear regression		x	x	
Analysis of variance (ANOVA)				x

5. Summary of results

5.1 Paper #I (Study #I):

Laryngeal movements during inspiratory muscle training in healthy subjects

Twenty healthy volunteers completed a training program with IMT (Respifit S©) with continuous laryngoscopy for visualization of the laryngeal response. We found that IMT can facilitate laryngeal abduction in healthy subjects, substantiating the PCA/diaphragm relationship [45]. However, a relatively large inter individual variability among the laryngeal response patterns during IMT was observed (Figure 10).

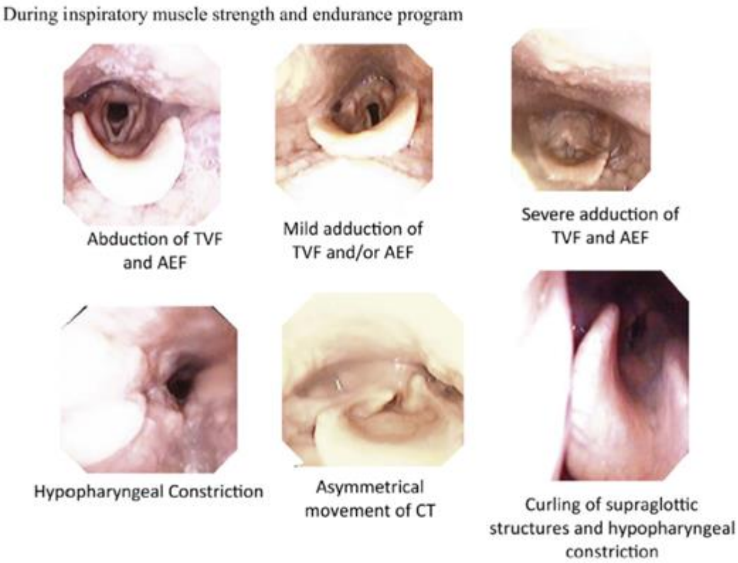


Figure 10: *Examples of laryngeal response patterns during IMST in healthy volunteers [2], reprinted with permission from Journal of Voice*

Abbreviations: TVF: true vocal folds; AEF: aryepiglottic folds; CT: cuneiform tubercle

The laryngeal response pattern to the muscular strength program (IMST) with resistance ≥ 80% of Pi_{max}, differed from that of the muscular endurance program (IMET) with resistance between 60-80% of Pi_{max}. During IMST, only six (32%) of the 19 subjects achieved maximal abduction of the laryngeal inlet throughout the complete inspiratory phase, four subjects had a moderate abduction. In two subjects, a moderate adduction was observed in the initial phase, one of whom developed a severe laryngeal adduction mid-inspiration, initiated by the vocal folds (glottic level), and followed by supraglottic structures. When lowering the resistance in the IMET program, laryngeal abduction was observed in 18 (90%) of 20 subjects. In the remaining two (10%) subjects, the larynx initially adopted a neutral position, followed by a moderate adduction in mid-inspiration in one of them. The findings underline the complexity of larynx, with muscles working together in a complex and coordinated way.

In conclusion, laryngoscopy provided visual confirmation of the relationship between the diaphragm and the PCA-muscle by visualization of laryngeal abduction during IMT in healthy subjects *(Research question #1).* Both IMST and IMET increased the laryngeal aperture in healthy subjects, but the application of medium resistance (IMET) seems superior to higher resistance (IMST) to achieve the desirable abductive response in all. *(Research question #2 and #3).* The findings are encouraging in terms of IMT as a treatment option for EILO and warrants further studies.

5.2 Paper #II (Study #II):

Exercise-induced laryngeal obstruction in athletes treated with inspiratory muscle training

Thirty athletes diagnosed with EILO completed a six-week training program with IMT, two were excluded due to insufficient datasets. Symptom improvement was reported in the majority. After IMT, 22/28 (79%) responded *yes* to a question if they felt their EILO problem had improved, whereas one reported that symptoms had worsen; 12/28 (43%) athletes responded *nothing* or *a bit* to the question "*How much are you bothered by your breathing difficulties?".* At exercise-testing after IMT, 5/28 (18%) athletes had an open larynx at maximum exercise intensity (CLE-sum scores 0 or 1). In 23/28 (82%) athletes, the CLE-sum scores improved, 8 of whom had a decrease in CLE-sum score ≥2, whereas 3/28 were unchanged. In two athletes, the CLE-sum score worsened, of whom one was judged by both raters as a classical supraglottic EILO and the other as a typical fast onset glottic EILO, characterized by anxiety and panic. A significant difference (before versus after) using mixed linear regression was observed only at maximal exercise intensity at the glottic laryngeal level (Figure 11).

In conclusion, perceived exercise induced symptoms and the laryngeal closure improved in most patients after IMT *(Research question #4 and #5).* Laryngeal improvements were seen mainly at the glottic level, suggesting that IMT might contribute to better control of particularly the vocal fold movements. We hypothesize that IMT may become an efficient conservative treatment tool in subgroups of EILO, and that one should probably be careful when applying IMT in predominant supraglottic EILO. The findings warrant for future randomized controlled trials that are needed to establish the scientific evidence of effect of IMT in EILO patients.

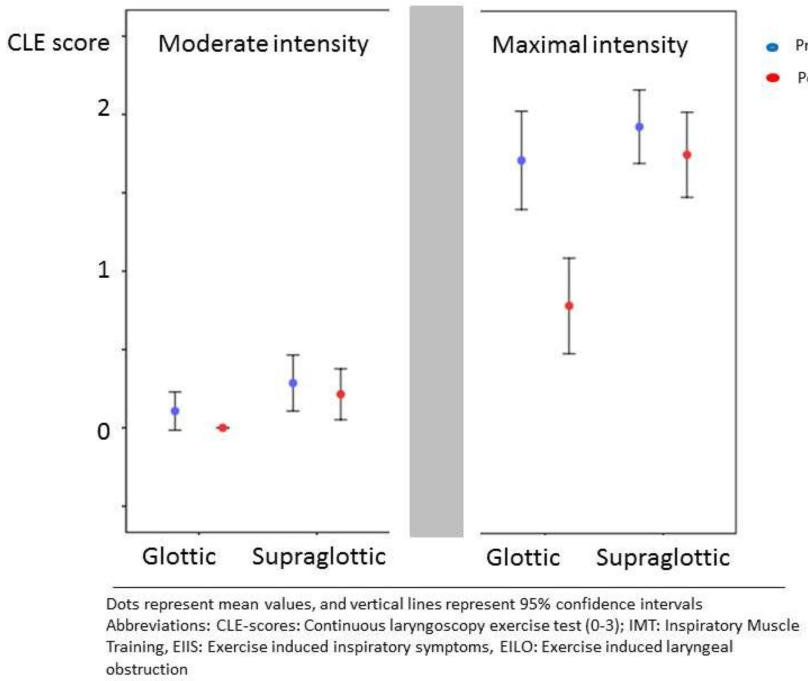


Figure 11: *Laryngeal obstruction scores according to Maat et al [1] in patients with EILO before and after six weeks training with IMT. Reprinted with permission BMJ Open Sports & Exercise Medicine.*

5.3 Paper #III (Study #III):

Severe exercise-induced laryngeal obstruction treated with supraglottoplasty

Sixty-one patients with severe supraglottic EILO were treated with supraglottoplasty during 2013-2015, twelve were excluded due to insufficient datasets and four excluded due to characteristics of laryngomalacia at rest. Thus, 45 were included in this retrospective study. Laryngoscopy at rest was normal in all subjects. After surgery, perceived subjective symptoms had improved in 38/44 (86%, one answer missing) and were unchanged in 5/44 (11%). All patients had significantly lower CLE sum-score after surgery, group mean reduced from 5.38 to 2.36; most improvements explained by reduced supraglottic scores at maximum exercise (CLE D-score) as expected (Figure 12). However, in 21/45 also the glottic obstruction decreased at maximum intensity exercise.

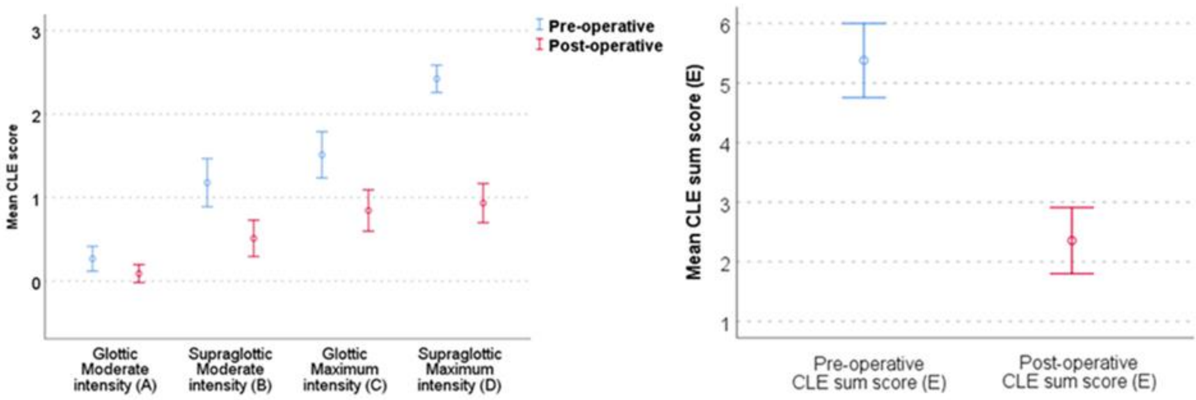


Figure 12: *Laryngeal obstruction scores according to Maat et al [1] in patients with EILO before and after supraglottoplasty, reprinted with permission from Frontiers in Surgery.*

The CLE sum-score was reduced by 2 or more in 38/45 (84%) patients. There were no signs of laryngeal obstruction at maximum exercise intensity, i.e. CLE sum-score 0 or 1 in 16/45 (36%). Complication rate in our data was 3% (2/65); a left vocal fold paresis that spontaneously resolved three years later and one with post-operative scarring with no symptoms at rest but breathing symptoms during exercise [196].

In conclusion, supraglottoplasty appears as a safe treatment for highly selected severe supraglottic EILO patients *(Research question #6).* Symptoms and laryngeal obstruction improved in the investigated patients after supraglottoplasty *(Research question #7 and #8).* Notably, supraglottoplasty might also improve glottic obstruction in patients with combined supraglottic and glottic obstruction. Risk of complications calls for careful selection of patients based on a multidisciplinary approach, thorough evaluation of the laryngeal obstruction (EILO subgroup) and with conservative treatment tested prior to surgery.

5.4 Paper #IV (Study #IV):

Clinical responses following inspiratory muscle training in exercise induced laryngeal obstruction

Altogether, 116 participants were identified from the *EILO-register*, response rates after 4-6 years were 23/58 (40%) and 32/58 (55%) in the IBA and IBA+IMT-group, respectively. At diagnosis, both groups rated symptoms similarly, but laryngeal scores were higher in the IBA+IMT-group. Shortly after IBA plus six weeks of IMT, 23/32 reported symptom improvements, associated with laryngeal improved, particularly with glottic changes (scores 1.7 vs. 0.3; p<0.001), contrasting unchanged laryngeal scores in 9/32 without symptom improvements (Figure 13).

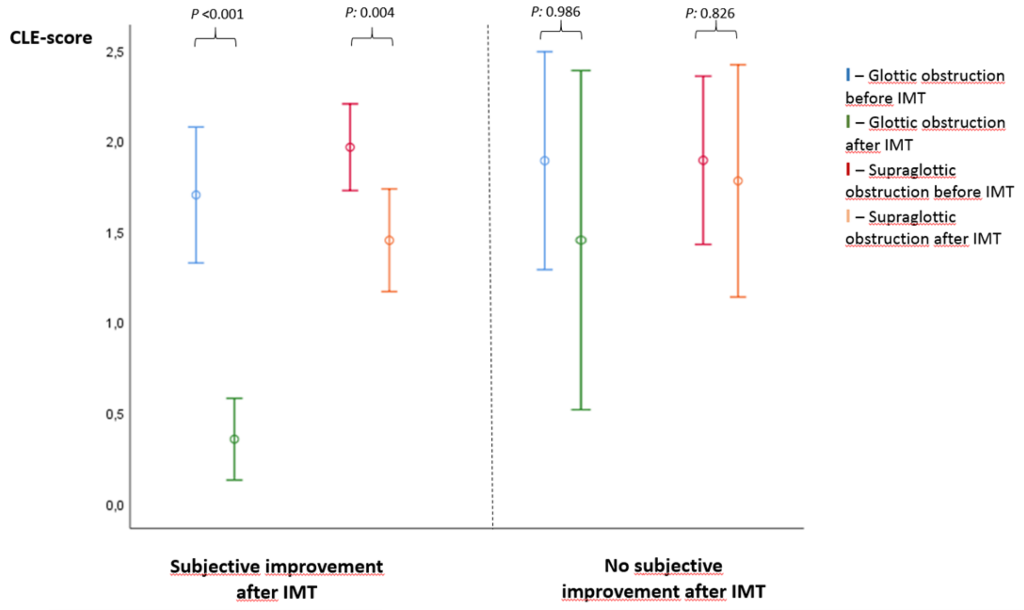


Figure 13: *Laryngeal obstruction (evaluated by CLE-scores at glottic and supraglottic level) in subjects with EILO before and after treatment with IBA plus six weeks of IMT. P values refer to mean change of glottic and supraglottic CLE-scores after six weeks of IMT.*

Following 4-6 years after diagnosis, exercise-related symptoms had improved, and activity level had decreased to similar levels in both groups irrespective of laryngeal findings and symptom reports shortly after IMT. Full symptom resolution was rare, only reported by 8/55 participants. Respiratory symptoms still disturbed most participants during exercise.

In conclusion, self-reported exercise symptoms and laryngeal outcome had improved shortly after IBA plus IMT, with EILO symptom improvements associated with glottic improvements *(Research question #9).* After 4-6 years, self-reported exercise symptoms had improved in both groups irrespective of initial treatment *(Research question #10).*

6. Discussion

The first part of the discussion will focus on the methodological aspects. Thereafter clinical implications of EILO, a general discussion of the main findings and suggestions for future research will follow.

6.1 Methodological considerations, strengths and limitations

To the best of our knowledge, this is the first thesis addressing evaluation of different treatment modalities in EILO patients in a short- and long-term perspective. Through clinical work and studies with an explorative nature, we have gained knowledge that will serve as a necessary basis for future controlled treatment trials. The strengths of this study was firstly that all patients were diagnosed with what is considered gold standard for diagnosing EILO, the CLE-test [79]. The same outcome measures were obtained under standardized conditions and applied in all the studies upon which this thesis is built, i.e., both *subjective* (self-reported symptoms) and *objective* (video-recordings of laryngeal response patterns) outcomes before and after treatment. The results were all stored in patients' charts, making the results available for later validation. The laryngeal obstruction was evaluated at both supraglottic and glottic level according to a pre-set scheme by experienced raters in a blinded procedure when possible. Recruitment of patients from the *EILO-register* in Study #III and #IV made it possible to include eligible participants from a heterogeneous patient population, and to conduct research on "real life patients" as they appear on a daily basis in clinical work, facilitating the generalizability of the findings. Finally, investigations of response patterns to different treatment modalities in EILO patients irrespective of subgroup or phenotype in an explorative and descriptive manner, is considered a strength as we do not properly understand to what extent different subgroups constitute separate disease entities or if they represent variations of one disease [118]. Thus, potential improvement from treatment in one EILO subgroup might be obscured by lack of improvement in another, and true effects may be concealed or difficult to detect.

However, the included studies also have limitations. Firstly, one large obstacle in EILO research, and thus also seen in our work, is that the correlation between perception of symptoms, the observed symptom presentation and the degree of laryngeal obstruction is likely individual and has not been properly established [79]. The studies that constitute the basis for this thesis includes a number of participants exceeding most previous research on EILO. Nevertheless, in order to establish solid data on the investigated issues, more patients need to be included in future studies. The pre-post study design without randomization before treatment and lack of control groups in Study #II and #III, are obvious weaknesses when evaluating treatment modalities. As with all small non-randomized un-controlled studies, the findings must therefore be cautiously interpreted. To some extent this uncertainty was compensated by the convenience-based and unbiased allocation to IMT in Study #II and #IV and the same thorough objective evaluation before and after treatment in Study #II, #III and #IV, making each participant serve as "their own control". A potential bias was that two different surgeons performed the supraglottoplasty procedure in Study #III, and that the IMT and IBA instructions were provided by three different physicians whose consistency was not established. However, these physicians know each other well, and they work together daily in a coordinated and standardized manner. Finally, a validated questionnaire to aid the self-reported symptoms would have been preferable, but this did not exist at the time the included participants were diagnosed (2013-2015) [79].

These issues regarding validity and reliability will be further discussed below.

6.1.1 Subjects and study sample

External validity describes the extent to which the results of a study can be generalized to others with the same condition [197]. The question is whether the results from the small groups examined can be generalized to the background population of all EILO patients. The study was conducted at the outpatient clinic in Bergen, receiving patients from all over Norway and is one of the centres in the world that has conducted most EILO examinations by date. The patients in Study #II were prospectively recruited from the clinic. In Study #III and #IV the patients were selected retrospectively by consecutive inclusions from a nationwide *EILO-register*. We acknowledge that a population derived from a tertiary centre might represent a potential referral bias, with patients with more severe symptoms or who are more "eager" to be investigated and treated. By nature, patients with EILO who reduce their activity level and thereby also reduce their symptoms, do not seek health care. Given these considerations, we conclude that recruitment from our outpatient clinic is considered representative for the EILO population who seeks treatment, as they are described in the literature with participants of all levels of exercise capacities [94, 198].

Our test sample seems representative of the EILO population regarding age [4, 11, 30-32]. The age distribution of healthy volunteers in Study #I (mean age: 24, range 21–29 years) was higher than mean age of the participants in Study #II and #III, possibly questioning the relevance for the age group in which EILO is most prevalent. However, all the examined volunteers had a normal larynx and no history of exercise induced inspiratory symptoms (EIIS), and therefore constituted a representative sample to investigate normal laryngeal response to IMT in a fully developed larynx. The laryngeal structures become more rigid with age [27, 199] and whether the larynx responds differently in different ages is unknown. One may speculate that a younger study population would have generated even more heterogeneous response than we found.

Regarding the gender distribution, there was a female predominance in all the included studies, and more so among those treated with second-line therapy (Study #II and #IV) than what has been described in the literature [30]. The reason for a possible female predominance in EILO patients is described in section 1.2.2, but one may question if males are underrepresented in referral for CLE-testing. The well described female tendency to report higher symptom scores in health-surveys [200] might contribute to more females being considered for second-line therapy (IMT).

To conclude on these issues, we hold that our recruited patient populations were representative for EILO patients who choose to seek treatment, and also comparable to patients described by others in the literature [30, 32, 198].

6.1.2 Sample size

Internal validity may be defined as a study's ability to measure what it set out to measure, and one must consider sources of error that might provide an alternative explanation for the findings; random errors, bias and confounding [201]. Adequate sample size is important to reduce risk of random error, explained as the variability of the data that cannot easily be explained [201]. Sample sizes in clinical studies depend on the availability of consenting participants. Due to few IMT apparatuses available and a training-period of 6-8 weeks, 51 patients underwent this treatment over a period of 2 years in Study #II. Not all participants were compliant to the training, and some did not want to perform a post-CLE-test. The patients completing the IMT protocol also formed the basis for the sample in Study #IV. The clinical data in Study #III were recorded retrospectively, and there were in some cases insufficiencies in the registration of data or technical problems with the video-recordings. Despite reminders we were unable to achieve a higher response-rate in Study #IV, and low response rates will of course introduce an unknown risk of responder bias due to a possible overrepresentation of adolescents with persistent experience of exercise-induced dyspnea. On the other hand, there might be patients who were so satisfied and happy with their treatment that they wished to provide feedback to the institution that helped solve their breathing problem. The characteristics regarding age, sex, symptom scores and CLE-scores did not differ between non-responders and participants at the time of diagnosis, but we had no way of establishing the motivation for participating at follow-up. The response rate is in line with some [202] but lower than other follow-up studies after treatment of EILO patients [144, 152, 155].

The low numbers complicated the statistical handling of the data, making the study vulnerable for particularly type II-errors; i.e., failure to detect significant differences that may have been present [187]. We therefore chose to provide descriptive reports of individual differences behind group means, in order to demonstrate the heterogeneity of the laryngeal responses and the patient group itself. We considered this a strength in this context. Confidence intervals were presented for all mean values, to address the issue of uncertainties [187]. A priori power calculations were difficult to perform as we did not know the distribution of the variables under investigation in this unstudied research field. There were some uncertainties with regard to the calculations performed with the CLE-scores being used as outcome measure (see Methods section), however the calculations suggest that adequate numbers of participants were included in Study #II and #III. Having said this, Study #II, #III and #IV still represent the largest patient series of their kind in the literature.

6.1.3 Study design

The knowledge on treatment modalities, especially conservative measures, in EILO patients were sparse and a descriptive explorative approach (or qvasi experimental design) was chosen. Thus, we prepared research questions to be explored rather than null hypotheses to be tested.

Cross-sectional study design (Study#I and #III)

A cross-sectional study design was used to document the status at a single time point or over a short period of time for each participant. The healthy volunteers in Study #I were only examined at one time point, acknowledging that the results obtained might differ from results obtained at another time point due to unrecognized confounders [203]. The definition cross-sectional pre-post study in Study #III may be discussed, as we evaluated two different examinations (over a short period of time), and in hindsight, a better term might have been "Retrospective pre-post study".

Pre-post study design (Study#II and #III)

In a pre-post study design, outcome(s) are measured before and after an intervention [204]. As each patient served as his/her own control, the method has the strength of temporality and to suggest that the outcome is impacted by the treatment. However, pre-post studies do not control other elements (confounders) that are also changing at the same time as the implemented treatment. Factors that might come into play and influence outcome are for example conditioning, or the effect itself of being tested and/or receiving a diagnosis and/or receiving a treatment, or by the simple fact that the participants take part in a study (the Hawthorne effect) [205]. Therefore, changes in relation to symptoms and laryngeal obstruction cannot be uncritically attributed to the intervention (IMT or supraglottoplasty). From a research perspective, the preferred design for evaluating effect of treatment is a randomized control trial [206]. A control group and formal randomization in Study #II and #III would clearly have strengthened the internal validity of the study by reducing risk of selection bias and confounders [203]. However, to set up a controlled study in the previously described "uncharted territory" of EILO treatment was not possible at the time the work leading to this thesis was commenced.

Retrospective identification from the EILO-register (Study #III and #IV)

Register-based studies are particularly suitable for investigating heterogeneous populations if the cover ratio is good [206], since they have broader inclusion criteria and fewer exclusion criteria. The *EILO-register* consists of patients diagnosed with EILO at Haukeland University Hospital after 2013. All participants in Study #III and #IV were recruited from this registry, thus reducing the risk of selection bias. A disadvantage of register-based studies is that both reporting from the patients and the clinicians are subject to bias [206], which we acknowledge and have tried to account for by using pre-set schemes in the clinical work. With retrospective follow-up studies there is a risk of bias by recall or in terms of positive and negative expectations related to the development of symptoms over time. This mechanism may have been involved in the IBA+IMT-group in Study #IV, where the significance of the breathing problem was scored lower when asked at diagnosis, compared to when retrospectively confronted with the same question at follow-up.

6.1.4 Outcome measures

Validity and reliability indicate how well a test measures an outcome. Reliability and repeatability are concepts that may be used interchangeable, and refers to the overall consistency of a measure [197, 207]. Validity refers to the ability of a test to measure what it is meant to measure [208]. The results of this thesis were based on application of both subjective rating (by the same questionnaires) of self-reported symptoms and a more objective evaluation of laryngeal obstruction (by CLE-scores) before and after treatment.

Self-reported symptoms

Self-reporting of symptoms may be questioned with respect to validity, as a fundamental shortcoming of all subjective approaches is the potential for misinterpretation of the questions or the potential of over- or understatements or socially desirable responding [200]; both by an “eager to please” mechanism or by an unrealistic expectation of effect from the treatment. Dyspnea is complex and by nature a subjective feeling [99], and the subjective perception of exercise symptoms also reflect real-life influence and how the patients cope with their breathing problem [101]. Therefore, such factors are probably important when self-reported symptoms are used in evaluating treatment responses in EILO. Validated questions that can be used to quantify self-reported symptoms of EILO are currently an unmet need in this research field [158], and certainly was at the beginning of this study [79]. Still no validated questionnaire exists in Norwegian. When this is said, the questionnaire applied has been utilized for many years at our clinic and addresses domains of sensory-perceptual experience and symptom impact or burden, as recommended when assessing dyspnea [101]. Six of the questions on symptoms are later validated in a context of monitoring and measuring symptoms of EILO [115]. Key items were retrieved from other respiratory contexts [117], and the questions are similar to questions applied in other studies [152, 155]. To be able to address longitudinal development, we applied the same questions at follow-up as were applied at diagnosis in Study #IV. Ideally, patients in Study #IV should have performed a new CLE-test at follow-up since poor physical condition is a common cause of dyspnea in studies that record symptoms from questionnaires [98, 102], and cannot be ruled out as a cause of respiratory complaints reported at follow-up in this study.

Symptom-presentation evaluated by an observer is reported to correspond well with the severity of laryngeal obstruction (CLE-score) [1], but perception of breathlessness is individual with a wide range of factors potentially contributing [91, 97] and does not necessarily correlate to the degree of obstruction [90, 120]. The pre-post CLE-test set-up allows for a more objective evaluation of the influence of the treatment, but the subjective self-reported symptoms convey the real-life benefits and must therefore be considered. Therefore, the strategy of reporting outcomes as self-reported symptoms combined with the CLE-test changes, enhances the validity of the results of the studies included in this thesis.

Laryngeal obstruction (the CLE-score)

Interobserver reliability addresses if a test provides the same results regardless of who carries out the measurement, and intra-observer reliability addresses if a test provides the same results when assessed twice or more by the same observer given that what we are measuring is not changing [197, 207]. The CLE-scoring system has been found reliable and valid to evaluate laryngeal function during exercise, with adequate inter-observer and intra-observer reliability of scores [1, 94]. A small study by Mirza and colleagues, found substantial agreement in supraglottic scores, but moderate agreement on glottic scores between two tests [94]. However, the scoring system has also been criticized for not classifying the severity of EILO in a reliable and robust way [135, 209]. The video-recordings are objective and stored for repeated evaluation, but the visual grading of the laryngeal obstruction is at risk of bias, because of the subjective evaluation by the rater. Visual grading of images is seen also in other fields of medicine, e.g., measurement of the ejection fraction in heart ultrasound [210]. Our research group has tried to solve some of these problems by using experienced raters from different professionals to evaluate the video-recordings, and to settle disagreements by consensus, as experience among the raters influence reliability [197, 207]. The raters of the CLE-tests were blinded in Study #I, #II and #IV to account for observer-bias.

To evaluate the degree of laryngeal obstruction from the two-dimensional view obtained from endoscopy is challenging. It is important to keep in mind that CLE scores only rate the relative degree of adduction of laryngeal structures. If the absolute size of the laryngeal aperture varies between people, this “relative approach” might be misleading as a similar degree of adduction might have different functional consequences in different people. Therefore, in our research group’s opinion, it is important to evaluate the development of the process that eventually leads to laryngeal obstruction and evaluate each larynx individually, as the point where increasing laryngeal obstruction becomes critical in terms of creating symptoms, is likely to differ between individuals, and – importantly – this point has not yet been established (Figure 4).

Concluding on these issues, it seems correct to state that the CLE-scoring system must currently serve as “the best available” method to rate the outcomes from a CLE-test, and that it provides a semi-objective outcome measure for evaluating laryngeal obstruction. It is important to apply the scoring system with caution, being aware of its shortcomings that could bias the assessment of treatment outcomes [135]. Development of a better scoring system is pending, both for diagnosis and evaluation of treatment, and was highlighted as a major research priority in the recent ERS/ELS statement [79].

The CLE-test and the test conditions

The CLE-score is based on video-recordings obtained from the CLE-test. Intra-subject reliability addresses if a test provides the same results if carried out twice or more in the same subject under the same conditions [197, 207]. It is important to reduce the factors that may contribute to the variability of measures like patient motivation, patient instructions, testing procedures, equipment/calibration errors and change in physical activity level.

The integrated testing system (CLE and full ergospirometry) with a computerized protocol was run according to manuals and was calibrated every morning and immediately before each test. Every test was performed under the same environmental conditions, with the same technician responsible for the test to be performed according to the standardized procedure. During the test, the technician pushed the participants to their limit of exercise tolerance. The applied computerized exercise-test protocol, consisting of gradual increases of both speed and angle from a slow flat initial walking phase, was considered satisfactory, as the participants ranged from sedentary individuals to top athletes. Treadmill exercise was preferred to cycle ergometer, as walking and running are familiar to most people. We used the same standardized protocol in all participants. However, some individuals may not be able to elicit their EILO symptoms due to the nature of their sport is different from a conventional treadmill test. One may speculate if individualized protocols would be more expedient, but at least the same protocol should be applied before and after treatment for adequate comparison. The influence of a laboratory setting versus “in the field” testing calls for exploration in future studies and has already been tested with rowing and swimming [50, 120].

A possible training effect of performing a second CLE-test could in theory have influenced the results as stated by Walsted and colleagues [135]. It is not our research group’s clinical experience that performing a CLE-test itself improves EILO and this has not been observed among patients performing multiple CLE-tests at our department (data not presented). To the best of our knowledge, the EILO literature does not suggest this either. Changes between tests in our studies were only significant for the variable “time to exhaustion”, which increased by a mean of 30 seconds from the first to the second test (data not tabulated). One may interpret this tendency for increased persistence at the second test as a risk of *under-detection* of EILO in the first test, i.e., not exercising long enough to achieve the exercise level when symptoms appear. Nevertheless, our findings are not based on the duration of the test but on comparisons of the laryngeal obstruction before and after at the same exercise intensity (compared by cardiopulmonary values), and not as isolated events. When this is said, the intra-subject reliability of the CLE-test needs to be established for future research [79].

Confounders such as change in physical activity level or the health condition of the subjects between the exercise tests (before and after treatment) may influence the results and lead to bias. A spirometry was conducted before each test to ensure that there was no airway obstruction to interfere with the results. If the patient was ill within the last 14 days, the test was postponed. In Study #III, where mean follow-up time varied, the aforementioned factors were impossible to eliminate completely, an obvious weakness of the study. However, ergospirometry performed in all made it possible to compare each larynx at the same exercise intensity and to ensure that the degree of exhaustion in both tests were adequate and similar in each subject to reduce some of these uncertainties. Additionally, the ergospirometry test made it possible to evaluate the self-reported physical activity level as self-reported instruments tend to overestimate the intensity and duration of physical activity [200].

6.2 Clinical implications and health consequences of EILO

Individuals ultimately diagnosed with EILO have often initially been misdiagnosed as exercise induced bronchoconstriction (EIB) [103, 104, 110], which presumably has resulted in mismanagement for long periods [108, 109]. In general, misdiagnosis and mismanagement of EILO may lead to patients' unnecessary seeking for health care and thus the generation of unnecessary costs, unnecessary investigations, and unnecessary medications with potential for unfortunate side effects [14, 162, 211]. EILO in athletes may lead to emotional stress, and over time prevent athletes from meeting the demands of their athletic participation [91, 157]. Dyspnea during exercise may also make young people reduce their level of physical activity and/or make them terminate their sports participation in an effort to minimize the frequency and severity of their breathing problem [147], a well described phenomenon in adolescents with EIB [104]. In a group with *undiagnosed* respiratory symptoms in subjects 12-14 years of age, 25% reported activity limitations [212]. Subjects with undiagnosed respiratory symptoms have reported more absence from school and low health-related quality of life compared to healthy peers [213].

Factors that affect physical activity are multifactorial, but young people moving from High School to college are at risk of inactivity and weight gain [214, 215]. The age period crucial in relation to the debut of EILO is also a vulnerable period for reduction in activity level, as many adolescents drop out of organized sporting activities [216]. The outcome and health gain of staying physically active, is substantial and strongly advocated, as well as important in a social context [214]. In Study #IV, most participants reported to have reduced their level of physical activity 4-6 years after diagnosis. Respiratory symptoms still disturbed most participants during exercise, however, fortunately the minority reported that their breathing problem prevented them from exercising.

Given the high prevalence of EILO, proper handling and follow-up of these young individuals seems important also from a public health perspective, as it might contribute to maintenance of a healthy level of physical activity [214, 217]. Although EILO symptoms usually ends when exercise is stopped, the desired outcome of our endeavours ought to be that breathing problems should not prevent adolescent from exercising.

6.3 Discussion of the main findings of the study

The present thesis demonstrates the complexity of the larynx, with large heterogeneities in response patterns to high intensity exercise, both before, during and after the applied treatment modalities in both asymptomatic volunteers and EILO patients. Our results indicate that both supraglottoplasty, inspiratory muscle training (IMT) and structured information with breathing advice (IBA) can improve symptoms and the laryngeal obstruction in short and long term in the majority of patients, with outliers in both directions.

To the best of our knowledge, we are the first to investigate the theoretical basis of applying IMT in EILO patients, by visualisation of the PCA/diaphragm relationship [21, 37, 39, 45] in Study #I. IMT enhanced the laryngeal opening during inspiration at rest in healthy volunteers. However, application of medium resistance seemed to be superior to higher resistance, as the former led to the desired laryngeal abduction in almost all participants. IMT in EILO patients reduced symptoms and laryngeal obstruction during high intensity exercise, with improvements seen mainly at the glottic level.

For EILO patients with severe supraglottic obstruction, supraglottoplasty is considered a safe procedure that reduces symptoms and laryngeal obstruction (as expected) at the supraglottic level. Interestingly, findings in Study #II and #III indicate that IMT also can be beneficial for supraglottic EILO (if not too severe), and that supraglottoplasty also can be beneficial for combined supraglottic and glottic EILO, with significant improvement observed also at the glottic level after surgery. Study #IV is the first long-term follow-up study after IMT used to treat EILO. Self-reported exercise-related symptoms were significantly reduced at follow-up

4-6 years after diagnosis and treatment with IMT and/or IBA. Symptom-scores at follow-up did not differ between those treated with IBA only and those who had additional six weeks of IMT. However, full resolution of breathing problems was rare.

The studies included in this thesis generate hypotheses of which treatment modality may be beneficial for different EILO subgroups. The findings substantiate the importance of classifying the level of obstruction as well as emphasizing the importance of proper evaluation after treatment and adequate follow-up to uncover persisting symptoms. What structures incites and perpetuates the pathology of a malfunctioning larynx, together with patient motivation, seems important when selecting treatment modality. The knowledge provided should be tested by others in randomized controlled studies.

6.3.1 Diversity of findings in EILO patients

In all examined participants, the larynx appeared normal at rest, but a large heterogeneity of laryngeal responses to exercise and treatment measures was observed. As seen in previous reports using the CLE-test [11, 107, 198], the most common EILO subgroup was supraglottic obstruction in a moderate degree as an inciting event, with adduction of the vocal folds appearing as a consequence or an associated phenomenon. Other subgroups were severe supraglottic obstruction with flaccid tissue without (or only minor) adduction of vocal folds. A few cases presented with primary adduction of the vocal folds as the major inciting event, with or without panic reactions. In some cases, the contribution of epiglottis to the sequence of events was probably important, based on clinical/empirical evaluation, but difficult to quantify as it is not involved in the scoring system applied [1]. Likely, there is also a floating clinical transition between the EILO subgroups. All of which seems important in development of treatment modalities tailored to subgroups.

Clinical symptom presentation and the degree of laryngeal obstruction seem to progress in a continuum, but to define a distinct cut-off for where the obstruction begins and the response ceases to be normal, is still challenging [207]. The findings throughout this thesis reveal inter-individual differences both in symptom perception and the laryngeal findings, as demonstrated in Study #IV were rating of symptoms were similar in both groups despite more advance laryngeal obstruction in the IBA+IMT group at time of diagnosis, thus supporting the notion of individual differences in relation to perception of when ventilation is limiting (Figure 4). However, the reported subjective improvement shortly after IMT in Study #IV was associated with laryngeal changes, especially at the glottic level. An impression after conducting the studies of this thesis, is that the level of physical activity and how the patients deal with their breathing problem also seem to be of relevance for the subjective rating of the symptoms.

Based on the experience obtained from conducting the work that this thesis is based on, and the heterogeneity that we have observed regarding the laryngeal response to high intensity exercise, caution is advocated when future studies are planned to evaluate treatment modalities in EILO patients.

6.3.2 Inspiratory muscle training

The symptomatic improvement after IMT seen in Study #II and #IV was consistent with previously published case-reports [147-149], and the findings substantiates the hypothesis that IMT targets glottic obstruction better than supraglottic obstruction in EILO patients.

Specificity of IMT

The laryngeal response to IMT in healthy normal individuals needed to be investigated in before applying IMT in EILO patients in subsequent studies. Study #I showed that IMT did in fact facilitate laryngeal abduction among the participants. The effect was poorer, and in some individuals even counterproductive, when applying high (≥80% of Pi_{max}) compared to lower resistances. Different response patterns seen during different inspiratory loads in Study #I is consistent with findings of high level of inherent biological variation in the structures of the upper airway in an MRI study [169]. The findings emphasize that opening of the laryngeal aperture can be more a question of training coordination, rather than the strength of the muscles. This phenomenon is consistent with training of skeletal muscles, i.e., that strength performance depends not only on the quantity and quality of the involved muscles, but also on the ability of the nervous system to appropriately activate specific movements and to better coordinate the activation of all relevant muscles [218, 219]. Thus, targeting the correct breathing technique with co-ordination of the inspiratory muscles seems crucial for effect of IMT in EILO patients and perhaps instructions with the laryngoscope in place could assist in achieving the wanted response.

Specificity of training in general implies that the training response/adaptations are tightly coupled with the nature of the applied stimulus [165, 220]. In short, muscles tend to respond to strength training stimuli (high intensity and short duration) by improving strength and to endurance-training stimuli (low intensity and long duration) by improving endurance [65, 218, 219]. In EILO patients, modalities that lead to laryngeal abduction and enhanced laryngeal patency seems preferable, and IMT may be beneficial both in enhancement of muscular strength and as a learning effect on co-ordination of inspiratory muscles leading to a more desirable breathing pattern. Thus, it seems reasonable to advocate a combined training program with elements of both endurance training (IMET) and strength training (IMST), contrary to only high-intensity training as applied in most published cases [147, 148]. However, concurrent training regimen (both strength and endurance training) may be sub-optimal because of targeting different specific adaptations [165], a phenomenon well established for peripheral skeletal muscles [221], and might also be the case with the inspiratory laryngeal muscles which may have influenced the outcome in Study #II and #IV.

The subjective and objective responses to IMT varied in Study #II and #IV. One may speculate if this was due to inclusion independent of EILO subgroups or that the patients that do not report symptomatic improvement shortly after IMT might be unable to engage the targeted inspiratory laryngeal muscle group, as seen in a few subjects in Study #I. Also, a potential concern when enhancing the ability of the diaphragm and inspiratory accessory muscles, is that the larynx remains the critical restriction of ventilatory capacity, i.e., “the bottleneck of the airways”. If the strength of the inspiratory muscles is enhanced by IMT, this might conceivably lead to increased inspiratory airflow and therefore increased intraluminal negative pressure in the larynx (the Bernoulli phenomenon) [54]. By this mechanism, flaccid supraglottic structures might get sucked inwards to a greater extent, which may lead to a posterior redirection of airflow and more turbulence, with alterations potentially influencing the intraluminal pressure also further down in the glottic area. In one of the patients with supraglottic obstruction worsening after IMT in Study #II, we could see that the redundant supraglottic tissue was adducted to a more severe degree during inspiration after IMT. One may therefore speculate if IMT may cause more harm than benefit in some cases of supraglottic EILO. We hypothesize that subgrouping EILO, would be a feasible approach in future studies addressing IMT to treat EILO patients.

IMT protocol (modality, resistance, frequency and duration)

Studies assessing IMT in EILO are scarce, and no standardized IMT protocol exist. The literature is also inconsistent in use of training modes, pressure settings, duration and number of repetitions for IMT protocols in healthy athletes [49, 221]. There are multiple possibilities regarding different devices, resistance loads, frequency etc. The breathing resistance applied in Study #I, #II and #IV were of flow-resistive loading, and the findings from these studies can not necessarily be transferred to other devices or other modes. Isokinetic training over threshold-training seems logical when targeting breathing technique, however, this is not scientifically verified. A training period of six-weeks has shown a plateau in inspiratory muscle strength and power [218], thus, the length of training chosen in our studies.

The resistance applied in the published case-reports on IMT and EILO varied from 25 to 80% of Pi_{max} [147-150]. A load set to 50% of Pi_{max} is known to improve thoracic inspiratory muscle function in healthy subjects [218], whereas optimal resistance in that respect is reported to be 60%-80% of Pi_{max}, declining at higher and lower intensities [67]. As little evidence on IMT and EILO existed before embarking on the included studies, we chose to use resistances as suggested by the manufacturer with an inspiratory load of $Pi_{max} \geq 80\%$ in the IMST program, and 60-80% of Pi_{max} in the IMET program, and to explore both IMST and IMET as previously mentioned. The equipment used, Respifit S®, is expensive and we could have chosen cheaper alternatives. However, availability and experience from our department made this the most convenient choice. In addition, the apparatus had a memory card to check for compliance of training.

An aggressive progression of IMT intensity to ensure a training overload has been stated essential for optimal adaption of exercise performance in healthy subjects [65], and similar to how IMT was used in some of the previous published EILO cases [147-149], with patients followed by numerous visits with adjustments of resistance related to Pi_{max}. In our study, adjustment of resistance half-way through the treatment period of six-weeks was not performed in all, perhaps a weakness of the study, as a progression of training intensity might have improved the results. The initial response after IMT was seemingly unrelated to symptom scores 4-6 years later in Study #IV, perhaps not unexpected, as muscle strength is reversible and changes over time [163], a potential improvement after IMT may also be transitory. The same phenomenon is also observed in healthy subjects after IMT [218].

To conclude on these issues, our findings are, with the uncertainties listed, a small step in moving forward in the field of conservative treatment of EILO. We were unable to fully test the opportunities that lie within inspiratory muscle training (IMT) and EILO regarding different resistances, training protocols, repeated interventions etc. We need targeted prospective controlled trials to address the issue of IMST versus IMET modality, the application of laryngoscopy during IMT instructions and to what extent scheduling repeated supervised training sessions might contribute to better results.

6.3.3 Supraglottoplasty on supraglottic EILO

Our findings are consistent with other reports [137, 152, 154, 155]; supraglottoplasty as treatment for severe supraglottic EILO show positive results on both perceived symptoms and laryngeal obstruction during exercise. The level of self-reported symptoms seemingly corresponded with the degree of laryngeal obstruction. One study by Maat and colleagues also demonstrated lasting results of both laryngeal obstruction and symptoms [152].

Surgical technique

Experience of the surgeons is an important factor for a successful outcome. The two senior consultants that performed the procedures in Study #III have experience with EILO patients and are familiar with micro-laryngeal surgery and the technique that was originally developed to treat severe congenital laryngomalacia, and they probably possess at least the same experience as the surgeons performing the procedure in other reports. However, this specific procedure has been performed in less than a hundred EILO patients at our hospital and only 133 cases are published internationally to date (Table 3). We found no difference in outcomes between the two surgeons. Some have argued that endoscopic supraglottoplasty should be performed in two phases to avoid supraglottic stenosis [10], however, our findings indicate that it is safe to perform the procedure in one operation. Moreover, one operation also reduces the risk of anaesthetic complications.

Diversity of laryngeal findings was also seen in the supraglottic EILO group with a variety of ways the supraglottic structures might adduct or close, suggesting a potential for different surgical approaches. Despite this, the same procedure was performed in all, except for epiglottotomy or epiglottopexy performed additionally in five patients with epiglottic involvement. The contribution of epiglottis in hampering the airflow during exercise has not been established [25], hence the effect of epiglottopexy or epiglottotomy is neither established. Thorough retrospective assessment of the post-operative CLE-test files in Study #III, suggest that in some cases, more of the redundant supraglottic tissue could have been removed. But as stated, a careful approach should be undertaken when performing surgery on otherwise healthy young people. Future controlled studies ought to evaluate different surgical techniques and should also compare postoperative CLE-test outcomes to some sort of sham-surgery.

Glottic improvement

The diversity of findings in Study #III substantiates the complexity of the larynx and EILO. By nature, most improvement after supraglottoplasty was observed at the supraglottic level, as this is the level of intervention. Glottic closure has previously been stated to be unresponsive to surgical treatment [138], a notion which our findings challenge. An interesting finding in Study #III was the resolution/improvement also of glottic obstruction that correlated with reduced supraglottic obstruction, a finding observed in half the patients after supraglottoplasty. This phenomenon was also reported by Maat and colleagues [152], and the finding cannot easily be explained. One may speculate that the removal of redundant supraglottic tissue leads to a wider supraglottic opening, which might lead to less turbulent airflow during high volume ventilation induced by the exercise, and thereby prevent/reduce adduction of the vocal folds (the Bernoulli principle). Another contributing factor may be that the arytenoid cartilages may be less exposed to medializing powers after the surgery. A recently published article presenting findings in 19 EILO patients operated with supraglottoplasty, reported that one patient had developed more pronounced glottic obstruction postoperatively, [137], for which we have no good explanation. Glottic improvement after supraglottoplasty could perhaps also be present in other studies, but due to low rate of postoperative endoscopic evaluation this effect may have been missed.

Relation to laryngomalacia

In order to avoid a mix between the adult type of laryngomalacia and EILO in Study #III, we retrospectively chose to exclude four patients who had characteristics of laryngomalacia at rest [61]. One may discuss if this was correct, as there was also a large heterogeneity of structural laryngeal findings observed in the included EILO patients; however, judged to be within normal limits. To what extent the anatomical characteristics of laryngomalacia influence laryngeal function during exercise has not been established [8, 61]. When this is said, although the diagnosis of laryngomalacia had not been acknowledged before showing up in our study, the four excluded patients were younger (mean age 8.8), had two anatomical characteristics of laryngomalacia (omega-shaped epiglottis and redundant aryepiglottic folds), and their symptoms had started at an early age. They all showed reduced CLE-scores and reported improvement in symptoms after surgery. Since it is clearly stated in the ERS/ELS/ACCP taxonomy that a diagnosis of ILO requires that the larynx appears normal unless exposed to the inducer, we found that the exclusion of this subgroup was correct. Probably there is a gradual transition of laryngeal characteristics from laryngomalacia to "normal laryngeal findings".

6.3.4 Side-effects of treatment

Cost-benefit analysis is necessary to perform for all treatment modalities [222]. Patients with EILO are otherwise healthy young people, with symptoms appearing only during exercise and any risks for complications should therefore be minimal. The term "safe" in Study #III was chosen to capture possible complications or adverse events after surgical interventions as this reflects the patient's safety.

IMT side-effects

Two patients in Study #II with supraglottic EILO worsened their supraglottic obstruction after IMT, and this can in the future perhaps be avoided with proper patient selection, avoiding patients with clearly redundant supraglottic tissue. None reported long-term side effects after IMT in Study #IV and none of the previously published case-reports on IMT and EILO reported any side-effects. A need for repeated training periods may be perceived as a strain and needs to be addressed properly in future studies. IMT is perceived as a "safe" treatment modality in EILO patients with relatively low cost.

Surgical side-effects

Follow-up of laryngeal function after supraglottoplasty performed in EILO patients has only been reported up to five years [181]. Despite the procedure being performed in multiple centres all over the world, only a total of 72 cases were published prior to Study #III [181, 182]. All studies report favourable results, with only two symptomatic complaints after surgery; one with dysphagia [154] and one with breathing difficulties while exercising in cold air [152], not provoked during the CLE-test in a laboratory setting. The procedure is based on the method performed in congenital laryngomalacia and has some established elements of risk, such as supraglottic stenosis and interarytenoid adhesion [223]. The experience of the surgeon and the choice of surgical technique (cold surgical techniques versus carbon dioxide laser) probably influences the risk of complications [137].

Study #III is the first to report on complications based on endoscopic examination in all after the procedure; with one patient exhibiting a self-limiting vocal fold paresis and one patient who had developed scarring. Voice or swallowing complications as side-effects did not occur. Even though the procedure is generally considered safe, our reports of complications calls for caution when treatment management are decided. Conservative treatment options should be tested beforehand. Nor should we ignore the possibility that low reporting of complications may be due to publication bias or to the few postoperatively CLE-tests that have been performed. This emphasizes the importance of evaluation of the postoperative larynx during exercise, compare to pre-operative findings, and correlate laryngeal findings to the individual’s symptoms.

6.3.5 Symptoms of EILO over time (Study #IV)

There is a lack of longitudinal EILO studies in the literature. To be assigned a correct diagnosis, reassurance and simply to provide IBA has been reported to be sufficient to obtain control over EILO symptoms in most patients [6, 14, 79, 159], but whether this symptom control is sustained over time is unknown. We found in Study #IV that self-reported symptoms after 4-6 years improved compared to at diagnosis irrespective of additional six weeks of IMT at time of diagnosis. However, full symptom resolution after 4-6 years was rare, and respiratory problems still disturbed most participants during physical activity. We found no evidence that the perceived breathing problem from EILO had resolved simply because the patients had reached adulthood, and this was consistent with the few other reports [152, 155, 224]. One may speculate if the low response rates might possibly be related to the benign nature of the condition, and that symptoms of EILO only appear during exercise which (regrettably) seems to be an activity most people reduce as they grow older, irrespective of their laryngeal response patterns. Further, it might be that individuals who still perceived their breathing during exercise to be problem were more likely to respond, as previously alluded to. However, one study re-examining EILO patients with a CLE-test after 20 years of age, observed unchanged laryngeal findings paralleled by declining physical activity and symptom severity over time [152]. Studies of older patients (over the age of 20 years) [137], support the notion that growth does not resolve EILO, and that improved symptoms might instead be due to reduced physical activity with age (lower ventilation requirements) and/or better coping with symptoms.

The improvements of self-reported symptoms after 4-6 years contribute to a positive view on these conservative treatment tools, particularly as regards glottic EILO. Answers from the IBA-group in Study #IV gives the impression that IBA might be sufficient in reducing symptoms over time in many with mild to moderate degree of laryngeal obstruction. The reported improvement after 4-6 years was unrelated to the findings shortly after IMT. Thus, the severity of diagnostic CLE-scores seemingly do not predict who will respond to IMT nor who will report high symptom scores after 4-6 years. We found an interesting tendency for less fear and possibly better symptom control in the IBA+IMT-group at follow-up, for which we have no good explanation.

7. Conclusion

Answer to research questions

Research question #1: Endoscopy provided visual confirmation of the relationship between the diaphragm and the PCA-muscle by visualization of laryngeal abduction during IMT in healthy subjects.

Research question #2 and #3: Both IMST and IMET increased the laryngeal aperture in the investigated healthy subjects, but the application of medium resistance (IMET) appeared superior to higher resistance (IMST) to achieve the desirable abductive response in all.

Research question #4: Self-reported exercise induced symptoms improved after six-weeks of IMT in selected EILO patients.

Research question #5: The laryngeal obstruction during exercise (evaluated by CLE-score) improved after six-weeks of IMT in selected EILO patients. The improvements were seen mainly at the glottic level.

Research question #6: Supraglottoplasty appeared as a safe treatment for highly selected severe supraglottic EILO patients.

Research question #7: Self-reported exercise induced symptoms improved after supraglottoplasty in the investigated EILO patients.

Research question #8: The laryngeal obstruction during exercise (evaluated by CLE-score) improved after supraglottoplasty in the investigated supraglottic EILO patients.

Research question #9: Self-reported exercise symptoms and laryngeal outcomes in EILO improved shortly after IBA plus IMT in selected EILO patients.

Research question #10: Self-reported exercise symptoms after 4-6 years was improved to similar levels in both groups, irrespective of additionally treatment with IMT at diagnosis.

Concluding remarks

This thesis has demonstrated that self-reported symptoms and laryngeal obstruction as observed and rated in CLE-tests, can improve after IMT or supraglottoplasty used to treat EILO patients.

Our findings substantiate the heterogeneity of laryngeal response patterns, in both asymptomatic volunteers and EILO patients. It is unlikely that *one* treatment will work in *all*, and the findings suggest proper subgrouping of EILO, individual treatment and follow-up. Future controlled studies are needed, and this work provides hypotheses and data such studies will be built on.

8. Perspectives

We propose that future clinical trials should address the hypothesis that EILO consists of different subgroups by stratifying the population under study at least according to glottic and supraglottic EILO. We need validated instruments with established intra-subject and inter-subject reliability to record self-reported perceived symptoms and grading of the laryngeal obstruction during CLE-tests. We need tools to establish the absolute dimensions of the laryngeal aperture, and the technique of measuring trans-laryngeal resistance might provide a future tool for better insight on the sequence of events and the absolute size of obstruction. This technique may serve as a functional objective continuous numerical measure of obstruction that can be compared to patients' symptom descriptions. Pressure measurements might also serve as a more objective outcome measure of laryngeal obstruction in future intervention studies.

Longitudinal studies after treatment with evaluation of the laryngeal obstruction are warranted in the future to evaluate development of EILO and possibly suggest who may need additional treatment to maintain physical activity.

8.1.1 The role of IMT in the future

- Lower resistances seem better than higher resistances, and endurance training better than high resistance (Pi_{max}) training. We suggest prospective controlled studies to investigate IMST vs. IMET *(Study #I).*
- We propose that IMT should be provided to EILO patients with mainly glottic obstruction or supraglottic EILO of only a mild degree *(Study #II and #IV).*
- If a patient reports worsening of symptoms after IMT, the training should cease, and a new evaluation of laryngeal obstruction is warranted (*Study #II*).
- We propose a randomized controlled trial to investigate the effects of simply providing IBA vs. additional treatment with IMT *(Study #I and #IV).*
- We propose that IMT instructions preferably should be performed with a laryngoscope in place to ensure the element of biofeedback and to ensure adequate engagement of muscles (*Study #I*).

- Adjustment of resistance during the intervention period is advised, and this should be tested in the future (*Study #II and #IV*).
- Repeated IMT periods can be a possible strategy if symptoms reoccur and should be tested in the future (*Study #IV*).

8.1.2 The role of supraglottoplasty in the future

Based on experience from Study #III:

- Properly controlled studies testing conservative treatment should be conducted before (and perhaps after) supraglottoplasty.
- We propose that surgery should only be offered patients with severe supraglottic obstruction, but glottic involvement may not be an exclusion criterion in cases were glottic involvement appears as a secondary phenomenon and to a less extent.
- After proper patient selection, controlled studies on supraglottoplasty and some sort of placebo surgery (or less extensive surgical procedures) should be conducted to try to reduce potential bias in our findings.
- We propose future testing of minimal invasive surgical procedures guided by the laryngeal response during exercise to reduce the invasiveness and risk of complications.
- Studies should be conducted to enhance the understanding of the role of the epiglottis in airway obstruction, and thus establish the role of epiglottotomy and/or epiglottopexy.

9. Source of data

1. Maat, R.C., et al., *Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations.* Eur Arch Otorhinolaryngol, 2009. **266**(12): p. 1929-36.
2. Sandnes, A., et al., *Laryngeal movements during inspiratory muscle training in healthy subjects.* J Voice, 2013. **27**(4): p. 448-53.
3. Heimdal, J.H., et al., *Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise.* Laryngoscope, 2006. **116**(1): p. 52-7.
4. Christopher, K.L. and M.J. Morris, *Vocal cord dysfunction, paradoxic vocal fold motion, or laryngomalacia? Our understanding requires an interdisciplinary approach.* Otolaryngol Clin North Am, 2010. **43**(1): p. 43-66, viii.
5. Christopher, K.L., et al., *Vocal-cord dysfunction presenting as asthma.* N Engl J Med, 1983. **308**(26): p. 1566-70.
6. Roksund, O.D., et al., *Exercise inducible laryngeal obstruction: diagnostics and management.* Paediatr Respir Rev, 2017. **21**: p. 86-94.
7. Lakin, R.C., W.J. Metzger, and B.H. Haughey, *Upper airway obstruction presenting as exercise-induced asthma.* Chest, 1984. **86**(3): p. 499-501.
8. Bent, J.P., 3rd, et al., *Pediatric exercise-induced laryngomalacia.* Ann Otol Rhinol Laryngol, 1996. **105**(3): p. 169-75.
9. Bittleman, D.B., R.J. Smith, and J.M. Weiler, *Abnormal movement of the arytenoid region during exercise presenting as exercise-induced asthma in an adolescent athlete.* Chest, 1994. **106**(2): p. 615-6.
10. Mandell, D.L. and E.M. Arjmand, *Laryngomalacia induced by exercise in a pediatric patient.* Int J Pediatr Otorhinolaryngol, 2003. **67**(9): p. 999-1003.
11. Roksund, O.D., et al., *Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways.* Respir Med, 2009. **103**(12): p. 1911-8.
12. Nordang, L., K. Norlander, and E.S. Walsted, *Exercise-Induced Laryngeal Obstruction-An Overview.* Immunol Allergy Clin North Am, 2018. **38**(2): p. 271-280.
13. Christensen, P.M., et al., *ERS/ELS/ACCP 2013 international consensus conference nomenclature on inducible laryngeal obstructions.* Eur Respir Rev, 2015. **24**(137): p. 445-50.
14. Shembel, A.C., M.J. Sandage, and K. Verdolini Abbott, *Episodic Laryngeal Breathing Disorders: Literature Review and Proposal of Preliminary Theoretical Framework.* J Voice, 2017. **31**(1): p. 125 e7-125 e16.
15. Patel, N.J., et al., *Concurrent laryngeal abnormalities in patients with paradoxical vocal fold dysfunction.* Otolaryngol Head Neck Surg, 2004. **130**(6): p. 686-9.

16. Olin, J.T. and E. Westhoff Carlson, *Exercise-Induced Laryngeal Obstruction and Performance Psychology: Using the Mind as a Diagnostic and Therapeutic Target.* Immunol Allergy Clin North Am, 2018. **38**(2): p. 303-315.
17. Liyanagedera, S., R. McLeod, and H.A. Elhassan, *Exercise induced laryngeal obstruction: a review of diagnosis and management.* Eur Arch Otorhinolaryngol, 2017. **274**(4): p. 1781-1789.
18. Christensen, P.M., et al., *ERS/ELS/ACCP 2013 international consensus conference nomenclature on inducible laryngeal obstructions.* Eur Respir Rev, 2015. **24**(137): p. 445-50.
19. Halvorsen, T., et al., *Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement.* Eur Respir J, 2017. **50**(3).
20. Heimdal, J.H., et al., *Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise.* Laryngoscope, 2006. **116**(1): p. 52-57.
21. Armstrong, W.B. and J.L. Netterville, *Anatomy of the larynx, trachea, and bronchi.* Otolaryngol Clin North Am, 1995. **28**(4): p. 685-99.
22. Fink, B.R., *Laryngeal Biomechanics.* Book, 1978.
23. Petcu, L.G. and C.T. Sasaki, *Laryngeal anatomy and physiology.* Clin Chest Med, 1991. **12**(3): p. 415-23.
24. Bartlett, D., Jr., *Respiratory functions of the larynx.* Physiol Rev, 1989. **69**(1): p. 33-57.
25. Belmont, J.R. and K. Grundfast, *Congenital laryngeal stridor (laryngomalacia): etiologic factors and associated disorders.* Ann Otol Rhinol Laryngol, 1984. **93**(5 Pt 1): p. 430-7.
26. McFadden, E.R., Jr. and D.K. Zawadski, *Vocal cord dysfunction masquerading as exercise-induced asthma. a physiologic cause for "choking" during athletic activities.* Am J Respir Crit Care Med, 1996. **153**(3): p. 942-7.
27. Wysocki, J., et al., *Measurements of pre- and postpubertal human larynx: a cadaver study.* Surg Radiol Anat, 2008. **30**(3): p. 191-9.
28. Castelli, W.A., P.C. Ramirez, and C.E. Nasjleti, *Linear growth study of the pharyngeal cavity.* J. Dent. Res, 1973. **52**(6): p. 1245-1248.
29. Kahane, J.C., *Growth of the human prepubertal and pubertal larynx.* J Speech Hear Res, 1982. **25**(3): p. 446-55.
30. Christensen, P.M., et al., *Exercise-induced laryngeal obstructions: prevalence and symptoms in the general public.* Eur Arch Otorhinolaryngol, 2011. **268**(9): p. 1313-9.
31. Nielsen, E.W., J.H. Hull, and V. Backer, *High prevalence of exercise-induced laryngeal obstruction in athletes.* Med Sci Sports Exerc, 2013. **45**(11): p. 2030-5.
32. Johansson, H., et al., *Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population.* Thorax, 2015. **70**(1): p. 57-63.
33. Baier, H., et al., *Relationships among glottis opening, respiratory flow, and upper airway resistance in humans.* J Appl Physiol Respir Environ Exerc Physiol, 1977. **43**(4): p. 603-11.

34. Cole, P., et al., *Resistance to respiratory airflow of the extrapulmonary airways.* Laryngoscope, 1993. **103**(4 Pt 1): p. 447-50.
35. Koufman, J.A. and C. Block, *Differential diagnosis of paradoxical vocal fold movement.* Am J Speech Lang Pathol, 2008. **17**(4): p. 327-34.
36. Ferris, B.G., Jr., J. Mead, and L.H. Opie, *Partitioning of Respiratory Flow Resistance in Man.* J Appl Physiol, 1964. **19**: p. 653-8.
37. Brancatisano, T., P.W. Collett, and L.A. Engel, *Respiratory movements of the vocal cords.* J Appl Physiol Respir Environ Exerc Physiol, 1983. **54**(5): p. 1269-76.
38. England, S.J., D. Bartlett, Jr., and J.A. Daubenspeck, *Influence of human vocal cord movements on airflow and resistance during eupnea.* J Appl Physiol Respir Environ Exerc Physiol, 1982. **52**(3): p. 773-9.
39. Tully, A., et al., *Influence of posterior cricoarytenoid muscle activity on pressure-flow relationship of the larynx.* J Appl Physiol (1985), 1991. **70**(5): p. 2252-8.
40. Fink, B.R., *The Human Larynx, a functional study*. Book, 1975.
41. Dion, G.R., R.L. Eller, and R.F. Thomas, *Diagnosing aerodynamic supraglottic collapse with rest and exercise flexible laryngoscopy.* J Voice, 2012. **26**(6): p. 779-84.
42. Beaty, M.M., J.S. Wilson, and R.J. Smith, *Laryngeal motion during exercise.* Laryngoscope, 1999. **109**(1): p. 136-9.
43. Hurbis, C.G. and J.A. Schild, *Laryngeal changes during exercise and exercise-induced asthma.* Ann Otol Rhinol Laryngol, 1991. **100**(1): p. 34-7.
44. Tervonen, H., et al., *Fiberoptic videolaryngoscopy during bicycle ergometry: a diagnostic tool for exercise-induced vocal cord dysfunction.* Laryngoscope, 2009. **119**(9): p. 1776-80.
45. Brancatisano, T.P., D.S. Dodd, and L.A. Engel, *Respiratory activity of posterior cricoarytenoid muscle and vocal cords in humans.* J Appl Physiol Respir Environ Exerc Physiol, 1984. **57**(4): p. 1143-9.
46. Norlander, K., et al., *Differences in laryngeal movements during exercise in healthy and dyspnoeic adolescents.* Int J Pediatr Otorhinolaryngol, 2020. **129**: p. 109765.
47. Carlsen, K.H. and M.L. Kowalski, *Asthma, allergy, the athlete and the Olympics.* Allergy, 2008. **63**(4): p. 383-6.
48. Dempsey, J.A., A. La Gerche, and J.H. Hull, *Is the healthy respiratory system built just right, overbuilt, or underbuilt to meet the demands imposed by exercise?* J Appl Physiol (1985), 2020. **129**(6): p. 1235-1256.
49. Illi, S.K., et al., *Effect of respiratory muscle training on exercise performance in healthy individuals: a systematic review and meta-analysis.* Sports Med, 2012. **42**(8): p. 707-24.
50. Panchasara, B., et al., *Lesson of the month: Rowing-induced laryngeal obstruction: a novel cause of exertional dyspnoea: characterised by direct laryngoscopy.* Thorax, 2015. **70**(1): p. 95-7.

51. Guenette, J.A. and A.W. Sheel, *Physiological consequences of a high work of breathing during heavy exercise in humans.* J Sci Med Sport, 2007. **10**(6): p. 341-50.
52. Naito, A. and S. Niimi, *The larynx during exercise.* Laryngoscope, 2000. **110**(7): p. 1147-50.
53. Strohl, K.P., et al., *Activation of upper airway muscles before onset of inspiration in normal humans.* J Appl Physiol Respir Environ Exerc Physiol, 1980. **49**(4): p. 638-42.
54. Bjornsdottir, U.S., et al., *Exercise-induced laryngochalasia: an imitator of exercise-induced bronchospasm.* Ann Allergy Asthma Immunol, 2000. **85**(5): p. 387-91.
55. Kashima, H.K., *Documentation of upper airway obstruction in unilateral vocal cord paralysis: flow-volume loop studies in 43 subjects.* Laryngoscope, 1984. **94**(7): p. 923-37.
56. Fajdiga, I., *Snoring imaging: could Bernoulli explain it all?* Chest, 2005. **128**(2): p. 896-901.
57. Maat, R.C., *Exercise-Induced Laryngeal Obstruction: Diagnostic procedures and therapy*, in *Department of Otolaryngology, Head & Neck Surgery Haukeland University Hospital, Bergen*. 2011, University of Bergen. p. 63.
58. Frank-Ito, D.O., et al., *Changes in aerodynamics during vocal cord dysfunction.* Comput Biol Med, 2015. **57**: p. 116-22.
59. Richter, G.T., et al., *Late-onset laryngomalacia: a variant of disease.* Arch Otolaryngol Head Neck Surg, 2008. **134**(1): p. 75-80.
60. Andersen, T., et al., *Laryngeal response patterns to mechanical insufflation-exsufflation in healthy subjects.* Am J Phys Med Rehabil, 2013. **92**(10): p. 920-9.
61. Hilland, M., et al., *Congenital laryngomalacia is related to exercise-induced laryngeal obstruction in adolescence.* Arch Dis Child, 2016. **101**(5): p. 443-8.
62. Fretheim-Kelly, Z., et al., *Feasibility and tolerability of measuring translaryngeal pressure during exercise.* Laryngoscope, 2019.
63. Walsted, E.S., et al., *Increased respiratory neural drive and work of breathing in exercise-induced laryngeal obstruction.* J Appl Physiol (1985), 2018. **124**(2): p. 356-363.
64. Moxham, J., *Respiratory muscle fatigue: mechanisms, evaluation and therapy.* Br J Anaesth, 1990. **65**(1): p. 43-53.
65. HajGhanbari, B., et al., *Effects of respiratory muscle training on performance in athletes: a systematic review with meta-analyses.* J Strength Cond Res, 2013. **27**(6): p. 1643-63.
66. Romer, L.M. and M.I. Polkey, *Exercise-induced respiratory muscle fatigue: implications for performance.* J Appl Physiol (1985), 2008. **104**(3): p. 879-88.
67. Janssens, L., et al., *The assessment of inspiratory muscle fatigue in healthy individuals: a systematic review.* Respir Med, 2013. **107**(3): p. 331-46.
68. Kenn, K. and R. Balkissoon, *Vocal cord dysfunction: what do we know?* Eur Respir J, 2011. **37**(1): p. 194-200.

69. Peters, E.J., et al., *Sinus computed tomography scan and markers of inflammation in vocal cord dysfunction and asthma.* Ann Allergy Asthma Immunol, 2003. **90**(3): p. 316-22.
70. Cukier-Blaj, S., et al., *Paradoxical vocal fold motion: a sensory-motor laryngeal disorder.* Laryngoscope, 2008. **118**(2): p. 367-70.
71. Phua, S.Y., et al., *The differential effect of gastroesophageal reflux disease on mechanostimulation and chemostimulation of the laryngopharynx.* Chest, 2010. **138**(5): p. 1180-5.
72. Maturo, S., et al., *Pediatric paradoxical vocal-fold motion: presentation and natural history.* Pediatrics, 2011. **128**(6): p. e1443-9.
73. Perkner, J.J., et al., *Irritant-associated vocal cord dysfunction.* J Occup Environ Med, 1998. **40**(2): p. 136-43.
74. Gimenez, L.M. and H. Zafra, *Vocal cord dysfunction: an update.* Ann Allergy Asthma Immunol, 2011. **106**(4): p. 267-74; quiz 275.
75. Hanks, C.D., et al., *Etiology of dyspnea in elite and recreational athletes.* Phys Sportsmed, 2012. **40**(2): p. 28-33.
76. Shembel, A.C., et al., *Perceptual Clinical Features in Exercise-Induced Laryngeal Obstruction (EILO): Toward Improved Diagnostic Approaches.* J Voice, 2018.
77. Stensrud, T., S. Berntsen, and K.H. Carlsen, *Humidity influences exercise capacity in subjects with exercise-induced bronchoconstriction (EIB).* Respir Med, 2006. **100**(9): p. 1633-41.
78. Stensrud, T., et al., *Bronchial hyperresponsiveness in skiers: field test versus methacholine provocation?* Med Sci Sports Exerc, 2007. **39**(10): p. 1681-6.
79. Halvorsen, T.W., E.S.; Bucca, C.; Bush, A.; Cantarella, G.; Friedrich, G.; Felix J.F.; Herth, F.J.F.; Hull, J.H.; Jung, H.; Maat, R.; Nordang, L.; Remacle, M.; and N.W. Rasmussen, J.A.; and Heimdal, J-H., *Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement.* European Respiratory Journal 2017. **50**.
80. Rundell, K.W. and B.A. Spiering, *Inspiratory stridor in elite athletes.* Chest, 2003. **123**(2): p. 468-74.
81. Smith, R.J., et al., *Exercise-induced laryngomalacia.* Ann Otol Rhinol Laryngol, 1995. **104**(7): p. 537-41.
82. Gessler, E.M., E.J. Simko, and J.H. Greinwald, Jr., *Adult laryngomalacia: an uncommon clinical entity.* Am J Otolaryngol, 2002. **23**(6): p. 386-9.
83. Walsted, E.S., et al., *Heredity of supraglottic exercise-induced laryngeal obstruction.* Eur Respir J, 2017. **50**(2).
84. Patterson, R., M. Schatz, and M. Horton, *Munchausen's stridor: non-organic laryngeal obstruction.* Clin Allergy, 1974. **4**(3): p. 307-10.
85. Powell, D.M., et al., *Paradoxical vocal cord dysfunction in juveniles.* Arch Otolaryngol Head Neck Surg, 2000. **126**(1): p. 29-34.
86. Freedman, M.R., S.J. Rosenberg, and K.B. Schmaling, *Childhood sexual abuse in patients with paradoxical vocal cord dysfunction.* J Nerv Ment Dis, 1991. **179**(5): p. 295-8.

87. Landwehr, L.P., et al., *Vocal cord dysfunction mimicking exercise-induced bronchospasm in adolescents.* Pediatrics, 1996. **98**(5): p. 971-4.
88. Walsted, E.S., *Evaluating diagnostic approaches in exercise-induced layngeal obstruction*, in *Respiratory Research Unit, Bispebjerg Hospital. Copenhagen*. 2017, University of Copenhagen, Faculty of Health and Medical Science. p. 47.
89. Weiler, J.M., et al., *Prevalence of bronchial hyperresponsiveness in highly trained athletes.* Chest, 1986. **90**(1): p. 23-8.
90. Johansson, H., et al., *Exercise-induced dyspnea is a problem among the general adolescent population.* Respir Med, 2014. **108**(6): p. 852-8.
91. Weinberger, M.M., *Etiology of exercise-induced dyspnea: not just exercise-induced asthma or vocal cord dysfunction.* J. Allergy Clin. Immunol, 2008. **121**(1): p. 269.
92. Morris, M.J., et al., *Vocal cord dysfunction in patients with exertional dyspnea.* Chest, 1999. **116**(6): p. 1676-82.
93. Diamond. E., K., C., Dugan, G., *Presentation and evaluation of vocal cord dysfunction.* Chest, 2000: p. 118(Suppl):199S.
94. Mirza, K.K., E.S. Walsted, and V. Backer, *Ergospirometry with concurrent fibre optic laryngoscopy: a randomised crossover study.* Eur Clin Respir J, 2017. **4**(1): p. 1399033.
95. Buchvald, F., et al., *Exercise-induced inspiratory symptoms in school children.* Pediatr Pulmonol, 2016. **51**(11): p. 1200-1205.
96. Ersson, K., et al., *Prevalence of exercise-induced bronchoconstriction and laryngeal obstruction in adolescent athletes.* Pediatr Pulmonol, 2020. **55**(12): p. 3509-3516.
97. Depiazzi, J. and M.L. Everard, *Dysfunctional breathing and reaching one's physiological limit as causes of exercise-induced dyspnoea.* Breathe (Sheff), 2016. **12**(2): p. 120-9.
98. Seear, M., D. Wensley, and N. West, *How accurate is the diagnosis of exercise induced asthma among Vancouver schoolchildren?* Arch Dis Child, 2005. **90**(9): p. 898-902.
99. Yorke, J., et al., *Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12.* Thorax, 2010. **65**(1): p. 21-6.
100. Banzett, R.B., et al., *Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research.* Eur Respir J, 2015. **45**(6): p. 1681-91.
101. Parshall, M.B., et al., *An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea.* Am J Respir Crit Care Med, 2012. **185**(4): p. 435-52.
102. Abu-Hasan, M., B. Tannous, and M. Weinberger, *Exercise-induced dyspnea in children and adolescents: if not asthma then what?* Ann Allergy Asthma Immunol, 2005. **94**(3): p. 366-71.
103. Weiss, P. and K.W. Rundell, *Imitators of exercise-induced bronchoconstriction.* Allergy Asthma Clin Immunol, 2009. **5**(1): p. 7.
104. Carlsen, K.H., *The breathless adolescent asthmatic athlete.* Eur Respir J, 2011. **38**(3): p. 713-20.
105. Rundell, K.W., et al., *Self-reported symptoms and exercise-induced asthma in the elite athlete.* Med Sci Sports Exerc, 2001. **33**(2): p. 208-13.

106. Weiler, J.M. and E.J. Ryan, 3rd, *Asthma in United States olympic athletes who participated in the 1998 olympic winter games.* J Allergy Clin Immunol, 2000. **106**(2): p. 267-71.
107. Roksund, O.D., et al., *Larynx during exercise: the unexplored bottleneck of the airways.* Eur Arch Otorhinolaryngol, 2015. **272**(9): p. 2101-9.
108. Kramer, S., et al., *Does treatment of paradoxical vocal fold movement disorder decrease asthma medication use?* Laryngoscope, 2017. **127**(7): p. 1531-1537.
109. Newman, K.B., U.G. Mason, III, and K.B. Schmaling, *Clinical features of vocal cord dysfunction.* Am. J. Respir. Crit Care Med, 1995. **152**(4 Pt 1): p. 1382-1386.
110. Hicks, M., S.M. Brugman, and R. Katial, *Vocal cord dysfunction/paradoxical vocal fold motion.* Prim Care, 2008. **35**(1): p. 81-103, vii.
111. Hull, J.H., et al., *High Prevalence of Laryngeal Obstruction during Exercise in Severe Asthma.* Am J Respir Crit Care Med, 2019. **199**(4): p. 538-542.
112. Abdelwahab, H.W., et al., *Prevalence of inducible laryngeal obstruction among patients diagnosed as bronchial asthma.* Adv Respir Med, 2020. **88**(2): p. 129-133.
113. Christopher, K.L., *Understanding vocal cord dysfunction: a step in the right direction with a long road ahead.* Chest, 2006. **129**(4): p. 842-3.
114. Weinberger, M. and M. Abu-Hasan, *Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma.* Pediatrics, 2007. **120**(4): p. 855-64.
115. Gartner-Schmidt, J.L., et al., *Development and validation of the Dyspnea Index (DI): a severity index for upper airway-related dyspnea.* J Voice, 2014. **28**(6): p. 775-82.
116. Traister, R.S., et al., *A novel scoring system to distinguish vocal cord dysfunction from asthma.* J Allergy Clin Immunol Pract, 2014. **2**(1): p. 65-9.
117. Fowler, S.J., et al., *The VCDQ--a Questionnaire for symptom monitoring in vocal cord dysfunction.* Clin Exp Allergy, 2015. **45**(9): p. 1406-11.
118. Hull, J.H., et al., *Laryngeal Dysfunction: Assessment and Management for the Clinician.* Am J Respir Crit Care Med, 2016. **194**(9): p. 1062-1072.
119. De Guzman, V., et al., *Validation of the dyspnea index in adolescents with exercise-induced paradoxical vocal fold motion.* JAMA Otolaryngol Head Neck Surg, 2014. **140**(9): p. 823-8.
120. Walsted, E.S., et al., *Laryngoscopy during swimming: A novel diagnostic technique to characterize swimming- induced laryngeal obstruction.* Laryngoscope, 2017.
121. Christensen, P.M. and N. Rasmussen, *Eucapnic voluntary hyperventilation in diagnosing exercise-induced laryngeal obstructions.* Eur Arch Otorhinolaryngol, 2013. **270**(12): p. 3107-13.
122. Turmel, J., et al., *Eucapnic voluntary hyperpnoea and exercise-induced vocal cord dysfunction.* BMJ Open Sport Exerc Med, 2015. **1**(1): p. e000065.
123. Bucca, C., et al., *Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction?* Lancet, 1995. **346**(8978): p. 791-5.

124. Bucca, C., et al., *Histamine hyperresponsiveness of the extrathoracic airway in patients with asthmatic symptoms.* Allergy, 1991. **46**(2): p. 147-53.
125. Bey, A., et al., *Bronchial or Laryngeal Obstruction Induced by Exercise?* Front Pediatr, 2017. **5**: p. 150.
126. Hira, H.S. and A. Singh, *Significance of upper airway influence among patients of vocal cord dysfunction for its diagnosis: Role of impulse oscillometry.* Lung India, 2009. **26**(1): p. 5-8.
127. Komarow, H.D., et al., *Vocal cord dysfunction as demonstrated by impulse oscillometry.* J Allergy Clin Immunol Pract, 2013. **1**(4): p. 387-93.
128. Watson, M.A., et al., *Clinical and lung-function variables associated with vocal cord dysfunction.* Respir Care, 2009. **54**(4): p. 467-73.
129. Walsted, E.S., et al., *Bronchial provocation testing does not detect exercise-induced laryngeal obstruction.* J Asthma, 2017. **54**(1): p. 77-83.
130. Gallena, S.J., et al., *The Effect of Exercise on Respiratory Resistance in Athletes With and Without Paradoxical Vocal Fold Motion Disorder.* Am J Speech Lang Pathol, 2015. **24**(3): p. 470-9.
131. Astorino, T.A., *Is the ventilatory threshold coincident with maximal fat oxidation during submaximal exercise in women?* J Sports Med Phys Fitness, 2000. **40**(3): p. 209-16.
132. Jain, S., et al., *Role of vocal cord function and dysfunction in patients presenting with symptoms of acute asthma exacerbation.* J Asthma, 2006. **43**(3): p. 207-12.
133. Christensen, P., et al., *Exercise-induced laryngeal obstructions objectively assessed using EILOMEA.* Eur Arch Otorhinolaryngol, 2010. **267**(3): p. 401-7.
134. Norlander, K., et al., *Comparison between two assessment methods for exercise-induced laryngeal obstructions.* Eur Arch Otorhinolaryngol, 2016. **273**(2): p. 425-30.
135. Walsted, E.S., et al., *Validity and reliability of grade scoring in the diagnosis of exercise-induced laryngeal obstruction.* ERJ Open Res, 2017. **3**(3).
136. Hull, J.H., *Multidisciplinary team working for vocal cord dysfunction: Now it's GO time.* Respirology, 2019.
137. Famokunwa, B., G. Sandhu, and J.H. Hull, *Surgical intervention for exercise-induced laryngeal obstruction: A UK perspective.* Laryngoscope, 2020.
138. Haines, J., J.H. Hull, and S.J. Fowler, *Clinical presentation, assessment, and management of inducible laryngeal obstruction.* Curr Opin Otolaryngol Head Neck Surg, 2018. **26**(3): p. 174-179.
139. Guglani, L., et al., *A systematic review of psychological interventions for adult and pediatric patients with vocal cord dysfunction.* Front Pediatr, 2014. **2**: p. 82.
140. Sullivan, M.D., B.M. Heywood, and D.R. Beukelman, *A treatment for vocal cord dysfunction in female athletes: an outcome study.* Laryngoscope, 2001. **111**(10): p. 1751-5.
141. Shaffer, M., et al., *Speech-Language Pathology as a Primary Treatment for Exercise-Induced Laryngeal Obstruction.* Immunol Allergy Clin North Am, 2018. **38**(2): p. 293-302.

142. Chiang, T., et al., *Exercise-induced paradoxical vocal fold motion disorder: diagnosis and management.* Laryngoscope, 2013. **123**(3): p. 727-31.
143. Patel, R.R., et al., *Evidence-Based Systematic Review: Effects of Speech-Language Pathology Treatment for Individuals With Paradoxical Vocal Fold Motion.* Am J Speech Lang Pathol, 2015. **24**(3): p. 566-84.
144. Doshi, D.R. and M.M. Weinberger, *Long-term outcome of vocal cord dysfunction.* Ann. Allergy Asthma Immunol, 2006. **96**(6): p. 794-799.
145. Olin, J.T., et al., *Therapeutic laryngoscopy during exercise: A novel non-surgical therapy for refractory EILO.* Pediatr Pulmonol, 2017. **52**(6): p. 813-819.
146. Rameau, A., et al., *Multidisciplinary approach to vocal cord dysfunction diagnosis and treatment in one session: a single institutional outcome study.* Int J Pediatr Otorhinolaryngol, 2012. **76**(1): p. 31-5.
147. Mathers-Schmidt, B.A. and L.R. Brilla, *Inspiratory muscle training in exercise-induced paradoxical vocal fold motion.* J Voice, 2005. **19**(4): p. 635-44.
148. Ruddy, B.H., et al., *Inspiratory muscle strength training with behavioral therapy in a case of a rower with presumed exercise-induced paradoxical vocal-fold dysfunction.* Int J Pediatr Otorhinolaryngol, 2004. **68**(10): p. 1327-32.
149. Dickinson, J., G. Whyte, and A. McConnell, *Inspiratory muscle training: a simple cost-effective treatment for inspiratory stridor.* Br J Sports Med, 2007. **41**(10): p. 694-5; discussion 695.
150. Clemm, H.S.H., et al., *The Heterogeneity of Exercise-induced Laryngeal Obstruction.* Am J Respir Crit Care Med, 2018. **197**(8): p. 1068-1069.
151. Sandnes, A., et al., *Exercise-induced laryngeal obstruction in athletes treated with inspiratory muscle training.* BMJ Open Sport Exerc Med, 2019. **5**(1): p. e000436.
152. Maat, R.C., et al., *Exercise-induced laryngeal obstruction: natural history and effect of surgical treatment.* Eur. Arch. Otorhinolaryngol, 2011.
153. Maat, R.C., et al., *Surgical treatment of exercise-induced laryngeal dysfunction.* Eur Arch Otorhinolaryngol, 2007. **264**(4): p. 401-7.
154. Mehlum, C.S., et al., *Supraglottoplasty as treatment of exercise induced laryngeal obstruction (EILO).* Eur Arch Otorhinolaryngol, 2016. **273**(4): p. 945-51.
155. Norlander, K., et al., *Surgical treatment is effective in severe cases of exercise-induced laryngeal obstruction: A follow-up study.* Acta Otolaryngol, 2015. **135**(11): p. 1152-9.
156. Baxter, M., et al., *Abnormal vocal cord movement treated with botulinum toxin in patients with asthma resistant to optimised management.* Respirology, 2014. **19**(4): p. 531-7.
157. Newsham, K.R., et al., *Paradoxical Vocal-Cord Dysfunction: Management in Athletes.* J Athl Train, 2002. **37**(3): p. 325-328.
158. Hull, J.H., K. Godbout, and L.P. Boulet, *Exercise-associated dyspnea and stridor: thinking beyond asthma.* J Allergy Clin Immunol Pract, 2020.

159. Johnston, K.L., et al., *The Olin EILOBI Breathing Techniques: Description and Initial Case Series of Novel Respiratory Retraining Strategies for Athletes with Exercise-Induced Laryngeal Obstruction.* J Voice, 2018. **32**(6): p. 698-704.
160. Graham, S., et al., *The Fortuitous Discovery of the Olin EILOBI Breathing Techniques: A Case Study.* J Voice, 2018. **32**(6): p. 695-697.
161. Kolnes, L.J., et al., *Physiotherapy improves symptoms of exercise-induced laryngeal obstruction in young elite athletes: a case series.* BMJ Open Sport Exerc Med, 2019. **5**(1): p. e000487.
162. Mathers-Schmidt, B.A., *Paradoxical vocal fold motion: a tutorial on a complex disorder and the speech-language pathologist's role.* Am J Speech Lang Pathol, 2001. **2001**(10): p. 111-125.
163. Leith, D.E. and M. Bradley, *Ventilatory muscle strength and endurance training.* J Appl Physiol, 1976. **41**(4): p. 508-16.
164. Bartolome, R.C., Stoller, J.K, Hollingsworth, H, *Respiratory Muscle training and testing in COPD.* Up to Date Database 2017.
165. McConnell, A.K. and L.M. Romer, *Respiratory muscle training in healthy humans: resolving the controversy.* Int J Sports Med, 2004. **25**(4): p. 284-93.
166. Hart, N., et al., *Evaluation of an inspiratory muscle trainer in healthy humans.* Respir Med, 2001. **95**(6): p. 526-31.
167. Harms, C.A., *Insights into the role of the respiratory muscle metaboreflex.* J Physiol, 2007. **584**(Pt 3): p. 711.
168. Jones, D.A., Round, J.M, *Skeletal Muscle in Health and Disease: A textbook of Muscle Physiology.* Manchester University Press, 1990(1990): p. pp. 98-115.
169. How, S.C., et al., *Acute and chronic responses of the upper airway to inspiratory loading in healthy awake humans: an MRI study.* Respir Physiol Neurobiol, 2007. **157**(2-3): p. 270-80.
170. Lindstedt, S.L., et al., *Do muscles function as adaptable locomotor springs?* J Exp Biol, 2002. **205**(Pt 15): p. 2211-6.
171. Archer, G.J., et al., *Inspiratory vocal cord dysfunction, a new approach in treatment.* Eur Respir J, 2000. **15**(3): p. 617-8.
172. Gaylord, J.N., S. Peterson, and J. Ray, *Struggling to Breathe: Inspiratory Muscle Training in Adolescent Athletes.* J Voice, 2020.
173. Wilson, J.J. and E.M. Wilson, *Practical management: vocal cord dysfunction in athletes.* Clin J Sport Med, 2006. **16**(4): p. 357-60.
174. Weinberger, M. and D. Doshi, *Vocal cord dysfunction: a functional cause of respiratory distress.* Breathe (Sheff), 2017. **13**(1): p. 15-21.
175. Kim, I.K., Cocoran, T., *Recent developments in heliox therapy for asthma and bronchiolitis.* Clin Pediatr Emerg Med, 2009. **2009;10(2):68-74.**
176. Denipah, N., et al., *Acute Management of Paradoxical Vocal Fold Motion (Vocal Cord Dysfunction).* Ann Emerg Med, 2017. **69**(1): p. 18-23.
177. Morrison, M., L. Rammage, and A.J. Emami, *The irritable larynx syndrome.* J Voice, 1999. **13**(3): p. 447-55.
178. Chemery, L., et al., *[Exercise-induced laryngomalacia].* Rev Mal Respir, 2002. **19**(5 Pt 1): p. 641-3.
179. McNally, P. and P. Greally, *Use of post-exercise laryngoscopy to evaluate exercise induced dyspnea.* Pediatr Pulmonol, 2010. **45**(10): p. 1037-9.

180. Orbelo D., C.S., *Exertional stridor: Differential diagnosis, investigation, and treatment based on serial exercise tests with flexible transnasal flexible laryngocopy*. Chest, 2014. **2014;145(3):556A**.
181. Heimdal, J.H., R. Maat, and L. Nordang, *Surgical Intervention for Exercise-Induced Laryngeal Obstruction.* Immunol Allergy Clin North Am, 2018. **38**(2): p. 317-324.
182. Siewers, K., V. Backer, and E.S. Walsted, *A systematic review of surgical treatment for supraglottic exercise-induced laryngeal obstruction.* Laryngoscope Investigative Otolaryngology, 2019.
183. Zeitouni, A. and J. Manoukian, *Epiglottoplasty in the treatment of laryngomalacia.* J Otolaryngol, 1993. **22**(1): p. 29-33.
184. Zalzal, G.H., J.B. Anon, and R.T. Cotton, *Epiglottoplasty for the treatment of laryngomalacia.* Ann Otol Rhinol Laryngol, 1987. **96**(1 Pt 1): p. 72-6.
185. Rickham, P.P., *Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki.* Br Med J, 1964. **2**(5402): p. 177.
186. Lovdata. *The Norwegian Health Research Act "Helseforskningsloven"*. 2008; Available from: https://lovdata.no/dokument/NL/lov/2008-06-20-44.
187. Bacchetti, P. and J.M. Leung, *Sample size calculations in clinical research.* Anesthesiology, 2002. **97**(4): p. 1028-9; author reply 1029-32.
188. Machin D, C.M., Walters S, *Medical statistics: a textbook for the health sciences.* Chichester, West Sussex, England: John Wiley & Sons Ltd; , 2007. **4th ed**.
189. Quanjer, P.H., et al., *Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society.* Eur. Respir. J. Suppl, 1993. **16**: p. 5-40.
190. Cumming, G.R., D. Everatt, and L. Hastman, *Bruce treadmill test in children: normal values in a clinic population.* Am J Cardiol, 1978. **41**(1): p. 69-75.
191. Kuna, S.T. and C.R. Vanoye, *Laryngeal response during forced vital capacity maneuvers in normal adult humans.* Am J Respir Crit Care Med, 1994. **150**(3): p. 729-34.
192. *ATS/ERS Statement on respiratory muscle testing.* Am J Respir Crit Care Med, 2002. **166**(4): p. 518-624.
193. Lang, T.A. and D.G. Altman, *Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines.* Int J Nurs Stud, 2015. **52**(1): p. 5-9.
194. Lydersen, S., *Statistical review: frequently given comments.* Ann Rheum Dis, 2015. **74**(2): p. 323-5.
195. Skovlund, E. and G.U. Fenstad, *Should we always choose a nonparametric test when comparing two apparently nonnormal distributions?* J Clin Epidemiol, 2001. **54**(1): p. 86-92.
196. Hilland, M., Engesæter, I., Sandnes A., Sandvik, L., Røksund, O.D., Heimdal, J.H., Halvorsen, T., Clemm, H.H., *Postoperative complications after surgical*

treatment for exercise induced laryngeal obstruction. Medicine & Science in Sports & Exercise 2013. **2017;49(5S):1047**.
197. Thomas, J.R.a.N., J. K., *Research Methods in Physical Activity*. 1990: Human Kinetics.
198. Walsted, E.S., Famokunwa B., Andersen L., Rubak S. L., Buchvald F., Pedersen L., Dodd J. W., Backer V., Nielsen K. G., Getzin A., Hull J. H. , *An international perspective on the demographic and clinical features of exercise induced laryngeal obstruction.* European Respiratory Journal, 2020. **202; 56: Suppl. 64, 1906.**
199. Fried, M.P., *The Larynx*. 1996, Mosby. p. 18-45.
200. Ekelund, U., Tomkinson, G., Armstrong, N., *What proportion of youth are physically active? Measurements issues, levels and recent time trends.* Br J Sports Med, 2011. **2011;45(11):859-65**.
201. Rothman K.J., G.S., Lash T.L., *Modern Epidemology*. 2008, Lippincott Williams & Wilkins.
202. Johansson, H., K. Norlander, and A. Malinovschi, *Increased prevalence of exercise-induced airway symptoms - A five-year follow-up from adolescence to young adulthood.* Respir Med, 2019. **154**: p. 76-81.
203. E., D., *Rehabilitation Research. Principles and Applications.* . Vol. 3 ed. . 2005, St. Louis, Missouri: Elseviers Saunders
204. Sedgwick, P. and N. Greenwood, *Understanding the Hawthorne effect.* BMJ, 2015. **351**: p. h4672.
205. Thiese, M.S., *Observational and interventional study design types; an overview.* Biochem Med (Zagreb), 2014. **24**(2): p. 199-210.
206. Gliklich R.E, D.N.A., Leavy M.B*, Registries for Evaluating Patient Outcome: A User's Guide (Internet)*. Vol. 3rd edition. 2014, Rockville (MD): Agency for Healthcare research and Quality (US).
207. Altman, D.G., *Practical Statistics for Medical Research*. 1995: Chapman&Hall.
208. Downing SM., Y.R., *Assessment in health professions education*. 2009, Routledge, New York.
209. Olin, J.T., et al., *Continuous laryngoscopy quantitates laryngeal behaviour in exercise and recovery.* Eur Respir J, 2016. **48**(4): p. 1192-1200.
210. Cole, G.D., et al., *Defining the real-world reproducibility of visual grading of left ventricular function and visual estimation of left ventricular ejection fraction: impact of image quality, experience and accreditation.* Int J Cardiovasc Imaging, 2015. **31**(7): p. 1303-14.
211. Traister, R.S., M.L. Fajt, and A.A. Petrov, *The morbidity and cost of vocal cord dysfunction misdiagnosed as asthma.* Allergy Asthma Proc, 2016. **37**(2): p. 25-31.
212. Yeatts, K., et al., *Health consequences associated with frequent wheezing in adolescents without asthma diagnosis.* Eur Respir J, 2003. **22**(5): p. 781-6.
213. Raza, A., et al., *What does adolescent undiagnosed wheeze represent? Findings from the Isle of Wight Cohort.* Eur Respir J, 2012. **40**(3): p. 580-8.
214. Pearson, N., et al., *Patterns of adolescent physical activity and dietary behaviours*. Int J Behav Nutr Phys Act, 2009. **6**: p. 45.

215. Wengreen, H.J. and C. Moncur, *Change in diet, physical activity, and body weight among young-adults during the transition from high school to college.* Nutr J, 2009. **8**: p. 32.
216. Ingebrigtsen, J.E.a.S., S.A, *Ungdoms fysiske aktivitet i Møre og Romsdal 2005.* Senter for idrettsforskning, NTNU samfunnsforskning AS, 2006. **Rapport 1/06**.
217. Corder, K., D. Ogilvie, and E.M. van Sluijs, *Invited commentary: Physical activity over the life course--whose behavior changes, when, and why?* Am J Epidemiol, 2009. **170**(9): p. 1078-81; discussion 1082-3.
218. Romer, L.M. and A.K. McConnell, *Specificity and reversibility of inspiratory muscle training.* Med Sci Sports Exerc, 2003. **35**(2): p. 237-44.
219. Menzes K.K.P, N.L.R., Avelino P.R., Polese J.C., Salmela L.F.T, *A Review on Respiratory Muscle Training Devices.* Journal of Pulmonary & Respiratory Medicine, 2018. **8**(2).
220. Morrissey, M.C., E.A. Harman, and M.J. Johnson, *Resistance training modes: specificity and effectiveness.* Med Sci Sports Exerc, 1995. **27**(5): p. 648-60.
221. Karsten, M., et al., *The effects of inspiratory muscle training with linear workload devices on the sports performance and cardiopulmonary function of athletes: A systematic review and meta-analysis.* Phys Ther Sport, 2018. **34**: p. 92-104.
222. Neumann, P.J. and G.D. Sanders, *Cost-Effectiveness Analysis 2.0.* N Engl J Med, 2017. **376**(3): p. 203-205.
223. Denoyelle, F., et al., *Failures and complications of supraglottoplasty in children.* Arch Otolaryngol Head Neck Surg, 2003. **129**(10): p. 1077-80; discussion 1080.
224. Ivancic, R., et al., *Reduced Asthma Medication Use after Treatment of Pediatric Paradoxical Vocal Fold Motion Disorder.* Laryngoscope, 2020.
225. Dunglison, R.D., *The practice of medicine.* Philadelphia: Lea and Blanchard, 1842: p. 257-258.
226. Osler, W., *The principles and practise of medicine, 4th edition.* New York: Appleton, 1902: p. pp. 1111-1122.
227. Pinho, S.M., et al., *Paradoxical vocal fold movement: a case report.* J Voice, 1997. **11**(3): p. 368-72.
228. Altman, K.W., et al., *Paradoxical vocal fold motion: presentation and treatment options.* J Voice, 2000. **14**(1): p. 99-103.

10. Appendix 1: Historical overview

Historical overview-EILO

1842 Dunglison:	the first description of “hysteric croup” in a medical textbook [225]
1869 Mackinzie:	the first visualization of abnormal movement of the vocal cords by laryngoscopy
1902 Osler:	Spasms of the laryngeal muscles during inspiration [226]
1974 Patterson:	“Munchausen stridor” as description of a woman with inspiratory stridor [84]
1982 Dowing:	Changes in respiratory movements of the human vocal cords during hyperpnea
1983 Christopher:	The true diagnosis of VCD/glottic obstruction, five patients with “uncontrolled asthma” [5]
1984 Lakin:	Exercise first recognized as a cause of VCD and first description of a solely supraglottic cause of the laryngeal obstruction visualized by laryngoscopy after exercise [7]
1994 Bittleman:	First endoscopic examination with exercise, the laryngoscopy after exercise revealed abnormal motion of the arytenoid region in one case [9]
1995 Smith:	CLE-test on bicycle in one patient with “adult onset laryngomalacia”, first report on supraglottoplasty [81]
1996 McFadden:	7 elite athletes with “chocking” sensation during exercise based on laryngoscopy or postexercise flow-volume loops [26]
1996 Landwehr:	7 athletes with VCD based on postexercise inspiratory FVL flattening [87]
1996 Bent:	Stationary bicycle during exercise [8]
1997 Pino:	CLE-test in one patient with “intermittent symmetric arytenoid motion” [227]
1999 Beaty:	Laryngoscopy during exercise on healthy subjects for evaluation of normal laryngeal function during exercise [42]
2006 Heimdal:	Continuous laryngoscopy exercise-test on a treadmill, the CLE-test, four patients [3]
2010 Christopher:	Periodic occurrence of laryngeal obstruction (POLO) divided into three categories: psychogenic, exertional and irritant (intrinsic and extrinsic) [4]

Overview of treatment of EILO before the included studies of this thesis

1995 Smith:	First report on supraglottoplasty in one patient with "adult onset laryngomalacia" [81].
1996 Bent:	Two patients with supraglottic EILO treated with supraglottoplasty [8].
2000 Archer:	Inspiratory muscle training (IMT) from an anaesthetic equipment used to treat symptoms of vocal cord dysfunction (VCD) at rest [171].
2000 Bjørnsdatter:	Two patients with supraglottic EILO treated with supraglottoplasty [54].
2000 Altman:	Report on 10 patients with ILO at rest, were five were treated with botulinum toxin and 2 with flexible nasopharyngoscopy biofeedback [228]
2001 Sullivan:	Report of 20 female athletes with EILO treated with speech therapy [140].
2002 Chemery:	One patient with supraglottic EILO treated with supraglottoplasty [178].
2002 Newsham:	Description of a therapeutic exercise program designed to promote diaphragmatic breathing in athletes with EILO, reported to "have been used successfully with collegiate and high school athletes and has been administered in both chronic and acute settings by speech-language pathologists and certified athletic trainers" [157].
2003 Mandell:	One patient with supraglottic EILO treated with supraglottoplasty [10].
2004 Ruddy:	First report on an athlete (rower) with EILO treated with IMT [148].
2005 Mathers-Schmidt:	An athlete with EILO treated with IMT for 5 weeks "on-off" for a total of 16 weeks, and one session of "patient education and relaxed-throat technique" [147].
2006 Doshi:	First report on use of Ipratropium Bromide inhaler before exercise to treat EILO [144].
2007 Dickinson:	An athlete with inspiratory stridor treated with IMT for 11 weeks [149].
2007 Maat:	Ten patients with supraglottic EILO treated with supraglottoplasty [153].
2008 Ritcher:	Three patients with supraglottic EILO treated with supraglottoplasty.
2010 McNally:	One patient with supraglottic EILO treated with supraglottoplasty.
2011 Maat:	Twenty-three (10 of them previously reported) patients with supraglottic EILO treated with supraglottoplasty and follow-up after 2-5 years, compared to 14 conservatively treated (with information and breathing advice) patients [152].
2012 Dion:	Three patients with supraglottic EILO treated with supraglottoplasty [41].
2013 Chiang:	Laryngeal control therapy in patients with paradoxical vocal fold movement disorders (PVFMD) [142].

11. Appendix 2: Questionnaires

SPØRRESKJEMA FOR FØRSTE CLE-TEST

Dato•……………… EILS nr•………..

1. SYKEHISTORIE

1.1 Falsk krupp episoder som liten?

□ Ofte (>10 ganger) □ Av og til (4-10 ganger) □ Sjeldent (0-3 ganger) □ Aldri hatt

1.2 Operert mandler/falske mandler?

□ JA □ NEI

1.3 Operasjoner i svelg eller strupe?

□ JA □ NEI

1.4 Operasjoner i nese-bihuler?

□ JA □ NEI

1.5 Dren i ører som barn?

□ JA □ NEI

1.6 Unormal lyd i pusten som spedbarn?

□ JA □ NEI □ VET IKKE

1.7 Hvor mange nedre luftveisinfeksjoner (bronkitt/lungebetennelse) har du hatt totalt?

□ Ofte (>10 ganger) □ Av og til (4-10 ganger) □ Sjeldent (0-3 ganger) □ Aldri hatt

1.8 Hvor mange øvre luftveisinfeksjoner (forkjølelser) har du hatt siste 12 mnd?

□ Ofte (>10 ganger) □ Av og til (4-10 ganger) □ Sjeldent (0-3 ganger) □ Aldri hatt

1.9 Hvor ofte har du vært hes de siste 12 mnd?

□ Ofte (>10 ganger) □ Av og til (4-10 ganger) □ Sjeldent (0-3 ganger) □ Aldri hatt

1.10 Hvor ofte har du vært plaget med nesetetthet de siste 12 mnd?

□ Ofte (>10 ganger) □ Av og til (4-10 ganger) □ Sjeldent (0-3 ganger) □ Aldri hatt

1.11 Er du plaget med halsbrann/sure oppstøt (gastroøsofagalrefluks)?

□ JA □ NEI

Hvis JA:

1.11.1 Har du fått påvist såkalt gastroøsofagal refluks? □JA □ NEI

1.11.2 Er du under utredning for halsbrann/sure oppstøt? □ JA □ NEI

2. ASTMA

2.1 Har du diagnosen astma (dvs. astmasymptomer utenom anstrengelse)?

□ JA □ NEI □ USIKKERT

2.1.1 Hvis ja, hvor gammel var du da du fikk diagnosen?

2.3 Har du diagnosen anstrengelsesutsløst astma?

□ JA □ NEI □ USIKKERT

2.4 Har du brukt astmamedisiner?

□ JA □ NEI

2.5.1 Hvilke astmamedisiner har du brukt?

____

____

2.5.2 Bruker du astmamedisiner nå (ca. de siste 2-3 månedene)?

□ JA □ NEI

2.5.3 Hvilke astmamedisiner bruker du nå?

____

____

2.5.4 Bruker du astmamedisin ved trening?

□ JA □ NEI

2.5.5 Bruker du astmamedisin utenom trening?

□ JA □ NEI

2.5.6 I hvor stor grad synes du astmamedisinene som du står på nå hjelper deg?

□ LITE/INGEN BEDRING □ NOE BEDRING □ STOR BEDRING

2.6 Hvor ofte har du hatt astmaanfall siste 12 mnd?

□ INGEN □ 1-3 GANGER □ 4-12 GANGER □ > 12 GANGER

3. HAR DU ANDRE SYKDOMMER/DIAGNOSER?

____

____

4. BRUKER DU ANDRE MEDISINER?

____

____

5. ANSTRENGELSE UTLØST PUSTEBESVÆR

5.1 Hvor gammel var du da pusteprobtemer ved anstrengelse startet? år________

5.2 Kan du beskrive første episode?

____

____

____

5.3 I hvilke situasjoner opplever du pusteproblemer?

□ I hvile
□ Ved lett anstrengelse (gange)
□ Ved moderat anstrengelse/trening (eks. jogging)
□ Ved kraftig anstrengelse (hard trening / konkurranse)

5.4 Er det noe som gjør at du lettere får slike pusteproblemer?

□ Sigarettrøyk □ Røykos □ Sterke lukter □ Psykisk belastning/stress □ Kulde
□ Fuktig/rått vær (tåke) □ Varme (Syden) □ Nesetetthet □ Annet:

____

5.5 Er det spesielle typer aktiviteter/treningsformer som lettere gir deg pusteproblemer?

____

5.6 Hvordan vil du beskrive problemet ditt? Hvor riktige er disse utsagnene for deg?

1=Aldri 2=Noen ganger 3=0fte 4=Nesten alltid 5=Hver gang

5.6.1. Jeg har problemer med innpust	1	2	3	4	5
5.6.2 Jeg har problemer med utpust	1	2	3	4	5
5.6.3. Jeg føler tetthet/smerte i hals	1	2	3	4	5
5.6.4 Jeg føler tetthet/smerte i bryst	1	2	3	4	5
5.6.5. Jeg får hes stemme	1	2	3	4	5
5.6.6. Jeg må stadig harke og kremte	1	2	3	4	5
5.6.7. Jeg har følelse av å bli kvalt	1	2	3	4	5
5.6.8. Jeg blir svimmel/kvalm og føler jeg besvimer	1	2	3	4	5
5.6.9. Problemet kommer raskt	1	2	3	4	5
5.6.10. Problemet går fort over	1	2	3	4	5
5.6.1 1. Jeg får følelse av panikk	1	2	3	4	5
5.6.12. Jeg får pustevansker når jeg er i fysisk aktivitet	1	2	3	4	5
5.6.13. Jeg hører unormal lyd/piping i pusten	1	2	3	4	5
5.6.14. Pusteproblemene hindrer meg i å trene	1	2	3	4	5
5.6.15. Jeg blir redd når pustevanskene opptrer	I	2	3	4	5
5.6.16. Jeg lar være å presse meg fysisk pga pustevanskene	1	2	3	4	5
5.6.17. Pustevanskene fortsetter også etter at jeg stopper/hviler	12		3	4	5
5.6.18. Jeg kan kontrollere pustevanskene når de kommer	1	2	3	4	5

5.7 Hvordan påvirker problemet deg i hverdagen?

1=Aldri 2=Noen ganger 3=0fte 4=Nesten alltid 5=Hver gang

5.7.1 Jeg har problemer med å løpe opp en trapp mellom to etasjer	1	2	3	4	5
5.7.2 Jeg har problemer med mosjon/gymnastikk	1	2	3	4	5
5.7.3 Jeg har problemer under lett trening	1	2	3	4	5

5.7.4 Jeg har problemer under hard trening eller idrettskonkurranser 1 2 3 4 5

5.7.5 Problemene er verre under konkurranser

enn ved tilsvarende hard trening 1 2 3 4 5

5,8 Hvordan opplever du pusteproblemet?

5.8.1. Pustebesværet er likt fra gang til gang □ JA □ NEI

5.8.2 Pustevanskene kan være en psykisk belastning □ JA □ NEI

5.8.3. Pustevanskene hindrer meg i å oppnå det jeg vil □ JA □ NEI

5.9 Dersom symptomene oppstår når du er fysisk aktiv, hvor lang tid tar det før pustevanskene forsvinner etter at du har stoppet aktiviteten.

□ 0-5 min. □ 5-15 min □ 15-45 min. □ 45 min. eller mer

5.10 Når du er fysisk aktiv, hvor mye er du plaget av dine pustevansker

□ Ikke noe □ Ganske mye □ Veldig mye □ Invalidiserende

5.11 Totalt sett i livet ditt, hvor mye er du plaget av dine pustevansker

□ Ikke noe □ Ganske mye □ Veldig mye □ Invalidiserende.

6. AKTIVITETSNIVÅ

6.1 Hvor mange ganger i uken driver du med idrett, eller mosjonerer du så mye at du blir andpusten og/eller svett?

□ Hver dag □ 4-6 ganger i uken □ 2-3 ganger i uken □ En gang i uken

□ En gang i mnd □ Mindre enn en gang i mnd □ Aldri

6.2 Hvor mange timer i uken driver du med idrett, eller mosjonerer du så mye at du blir andpusten og/eller svett?

□ Ingen □ omtrent $^{1}/2$ time □ omtrent 1 time □ omtrent 2-3 timer

□ omtrent 4-6 timer □ 7 timer eller mer

6.3 Hvilken type idrett driver du med?

6.3.1 På hvilket nivå?

□ Mosjon □ Lokallag □ Regionalt nivå □ Nasjonalt nivå
□ Internasjonalt

6.3.2 Har du trappet ned aktivitetsnivået ditt grunnet problemer?

□ JA □ NEI

6.3.3. Hvis Ja, på hvilken måte har du endret aktivitetsnivået?

□ Måtte slutte med idrett □ Måtte trappe ned på nivå □ Har skiftet type idrett

6.4 Hvis jeg ikke hadde disse pusteproblemene, ville jeg vært mer fysisk aktiv

□ JA □ NEI □ Vet ikke

QUESTIONNAIRE

FOLLOW-UP OF PATIENTS WITH EXERCISE-INDUCED RESPIRATORY SYMPTOMS

Please answer all questions, and answer as to how you are feeling now.

1. Which treatment did you receive? (Tick as many boxes as appropriate)

¤ Information (about the condition) only
¤ Inspiratory muscle training
¤ Speech therapy
¤ Surgery
¤ Treatment at another clinic

2. How have your breathing problems changed since your first appointment (Q-A.1-8)?

Q-A.1 The breathing problem have got worse	□ Yes	□ No	□ Unsure
Q-A.2 Unchanged, they bother me about as much as before	□ Yes	□ No	□ Unsure
Q-A.3 Unchanged, but I have learnt to live with them	□ Yes	□ No	□ Unsure
Q-A.4 They cause me less problems because I am less active	□ Yes	□ No	□ Unsure
Q-A.5 They cause me less problems because I avoid activities that provoke symptoms	□ Yes	□ No	□ Unsure
Q-A.6 Symptoms are not as severe as before	□ Yes	□ No	□ Unsure
Q-A.7 The breathing problem has improved	□ Yes	□ No	□ Unsure
Q-A.8 I no longer have a breathing problem	□ Yes	□ No	□ Unsure

3.1 Considering all aspects of life, how much did your breathing problems effect you before you received treatment (Q-B.1)?

□ Not at all □ A little □ Quite a lot □ A great amount □ Crippling

3.2 Considering all aspects of life, how much do your breathing problems effect you now (Q-B.2)?

□ Not at all □ A little □ Quite a lot □ A great amount □ Crippling

4. How would you describe your breathing problems NOW (Q1-18)?

		Never	Occasionally	Often	Nearly always	Always
Q.1.	I have problems breathing in	1	2	3	4	5
Q.2.	I have problems breathing out	1	2	3	4	5
Q.3.	I feel tightness/pain in my throat	1	2	3	4	5
Q.4.	I feel tightness/pain in my chest	1	2	3	4	5
Q.5.	I get a hoarse voice	1	2	3	4	5
Q.6.	I frequently have a cough/clear my throat	1	2	3	4	5
Q.7.	I feel like I'm being choked	1	2	3	4	5

Q.8. I become dizzy, nauseous and feel like I'm going to faint	1	2	3	4	5
Q.9. The symptoms come on fast	1	2	3	4	5
Q.10. The symptoms quickly resolve	1	2	3	4	5
Q.11. I feel panic	1	2	3	4	5
Q.12. I have problems breathing when I am physically active	1	2	3	4	5
Q.13. I can hear unusual or peeping sounds when I breathe	1	2	3	4	5
Q.14. My symptoms prevent me from training/exercising	1	2	3	4	5
Q.15. I become afraid when I get symptoms	1	2	3	4	5
Q.16. My symptoms prevent me pushing myself when exercising	1	2	3	4	5
Q.17. My breathing problems continue even after I have stopped exercise/rested	1	2	3	4	5
Q.18. I can control my symptoms when I get them	1	2	3	4	5

5. How many hours per week do you play sport/ exercise at an intensity that makes you breathless and / or sweaty.

□ None
□ About 30 minutes
□ About 1 hour
□ About 2-3 hours
□ About 4-6 hours
□ 7 hours or more

6.1 What sport do you play?____

6.2 At what level?

□ For personal training
□ Local
□ Regional
□ National
□ International

7. Have you experienced any side effects/ negative symptoms after treatment for your exercise induced breathing problems?

□ no prolonged side effects / problems
□ Yes
If yes, please describe:

Thank you for taking the time to answer!

12. Appendix 3: Paper I-IV

Paper I (Study #I)

Laryngeal Movements During Inspiratory Muscle Training in Healthy Subjects

***Astrid Sandnes, †,‡Tiina Andersen, §Magnus Hilland, §Thor Andre Ellingsen, *,‖Thomas Halvorsen, §,¶John-Helge Heimdal, and *,‖Ola Drange Røksund,** *†‡§‖¶*Bergen, Norway*

Summary: Background. Inspiratory muscle training (IMT) has been used to treat patients with exercise-induced vocal cord dysfunction (VCD); the theoretical basis being the close relationship between the diaphragm and the posterior cricoarytenoid muscle, which is the main abductor of the larynx. Before launching a treatment protocol in patients with VCD, we aimed to substantiate this theory by performing laryngoscopy in healthy subjects during standardized IMT programs.

Methods. Twenty healthy volunteers at mean age 24 years were examined with video-recorded continuous transnasal flexible laryngoscopy while performing standardized training programs using a resistive loading IMT device (Respifit S). All subjects were exposed to two modes of training, that is, the resistance set to generate mouth pressures ≥80% of the maximal attainable inspiratory mouth pressure (PI_{max}) and 60–80% of PI_{max}. Laryngeal movements were scored in retrospect from the video recordings by a senior laryngologist.

Results. At pressure settings of ≥80% of PI_{max}, laryngeal movements could not be assessed in one subject. Abduction was observed in 10 (53%) subjects, six to a maximal extent and four to a moderate extent. At pressure settings of 60–80% of PI_{max}, abduction was observed in 18 (90%) subjects, seven to a maximal extent and 11 to a moderate extent.

Conclusions. IMT can produce laryngeal abduction in healthy subjects, and training programs may conceivably contribute positively in patients suffering from laryngeal adduction during exercise. Individual response patterns varied between subjects and individualized programs seem crucial for effect. Use of high resistances seemed to be counterproductive.

Key Words: Vocal cord dysfunction–Inspiratory muscle training–Laryngeal obstruction–Exercise.

INTRODUCTION

Central airway obstruction during exercise is not uncommon in healthy individuals, and prevalence rates as high as 7.5% have been reported in unselected populations.[1,2] The obstruction usually presents with inspiratory breathing symptoms such as prolonged and/or noisy inspiration, shortness of breath, and a sense of throat or chest tightness in the initial phase, whereas high-pitched inspiratory noise or stridor, hyperventilation, or panic reactions tend to represent an end point forcing most patients to stop the exercise session.[3,4] Collectively, this clinical presentation has been labeled exercise-induced inspiratory symptoms (EIIS). In most cases, EIIS is related to obstruction of laryngeal structures (Figure 1).[4] Several terms have been applied to label this obstruction at the laryngeal level, of which exercise-induced vocal cord dysfunction (VCD) or exercise-induced laryngeal obstruction (EILO) have been used frequently, the latter principally being used throughout this article.[3–5]

There is little robust evidence about effects of intervention to reduce airway obstructions originating in the larynx during exercise. Speech therapy has been reported as a mainstay,[6–13] while psychotherapy,[14] relaxation therapy,[15] hypnosis,[16] biofeedback techniques,[17,18] anticholinergic aerosols,[19] and surgical laser supraglottoplasty[20–24] have also been advocated. The common goal of these interventions has been to increase the size of the laryngeal inlet during the increasing airflow velocity induced by increasing exercise intensity.

Inspiratory muscle training (IMT) has been reported to help patients with symptoms attributed to VCD in some case reports.[25–27] IMT is a simple and cost-effective treatment used to strengthen the diaphragm and enhance breathing efficiency in several medical scenarios, such as chronic obstructive pulmonary disease,[28] asthma, cystic fibrosis, heart failure, spinal cord injuries, and muscular dystrophy,[29] and also in athletes.[30,31] The theoretical basis for using IMT in laryngeal obstruction is the coupled and phasic relationship that exists between the diaphragm and the posterior cricoarytenoid (PCA) muscle, the main abductor of the vocal folds.[32,33] Contraction of the PCA muscle slides and rotates the vocal processes laterally, thereby increasing the horizontal dimension of the glottic aperture.[34] Thereby, IMT could conceivably contribute to a more effective and better-controlled laryngeal abduction during exercise,[27] but this putative mechanism has not been observed by objective methods. Therefore, a visualized confirmation was needed before introducing IMT

Accepted for publication February 26, 2013.
Conflict of interest statement: None.
Funding: This work was supported by Haukeland University Hospital and University of Bergen.
Abstract and poster presentation at the European Respiratory Society Meeting; 24-28 September 2011; Amsterdam, The Netherlands.
From the *Department of Pediatrics, Haukeland University Hospital, Bergen, Norway; †Department of Physiotherapy, Haukeland University Hospital, Bergen, Norway; ‡Norwegian Centre of Excellence for Home Mechanical Ventilation, Bergen, Norway; §Department of Otolaryngology-Head and Neck surgery, Haukeland University, Hospital, Bergen, Norway; ‖Section for Pediatrics, Institute of Clinical Medicine, University of Bergen, Bergen, Norway; and the ¶Institute of Surgery, University of Bergen, Bergen, Norway.
Address correspondence and reprint requests to Ola Drange Røksund, Department of Pediatrics, Haukeland University Hospital, N-5021 Bergen, Norway. E-mail: odro@helse-bergen.no
Journal of Voice, Vol. 27, No. 4, pp. 448-453
0892-1997/$36.00

http://dx.doi.org/10.1016/j.jvoice.2013.02.010

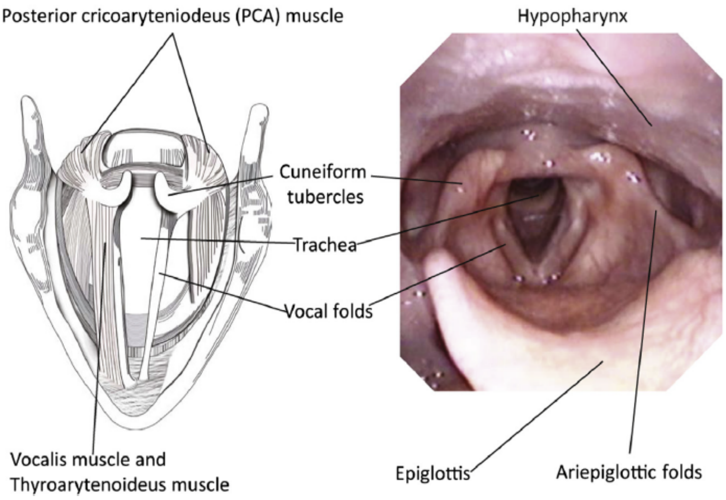


FIGURE 1. Laryngeal anatomy in healthy subjects.

as a clinical trial. We have conducted a pilot study, aiming to investigate laryngeal response pattern(s) during IMT in healthy subjects using laryngoscopic evaluation and imaging.

METHODS

Study design, subjects, and equipment

This was a descriptive, observational study of 20 healthy medical students with no history of exercise-related breathing problems and who volunteered to participate in the study. The study was approved by the Committee on Medical Research Ethics of Western Norway and informed written consent was obtained from participants.

A transnasal flexible fiberoptic laryngoscope (Olympus ENF-V2; Olympus, Tokyo, Japan), diameter 3.5 mm, was used to document laryngeal response pattern. Continuous video recording from the laryngoscope and a film of the upper part of the body and breath sounds were simultaneously recorded throughout the IMT sessions and stored for later evaluation.

Respifit S (Biegler GmbH, Mauerbach, Austria) was used to measure the maximal inspiratory mouth pressure (PI_{max}) and to provide exact settings of the resistance during the IMT sessions.

Spirometry was performed with Vmax 22 spirometer (SensorMedics, Yorba Linda, CA) according to guidelines.[35] Forced vital capacity and forced expiratory volume in one second were recorded and reported as percentages of predicted.[36]

Performing the IMT

The laryngoscope was introduced after application of a decongestive nasal spray (Rhinox 0.25 mg/ml) and local anesthesia (Xylocaine 40 mg/ml) and secured in a position allowing for a good view of the laryngeal entrance, including supraglottic structures and the vocal folds. Thereafter, PI_{max} was measured with the Respifit S, using the best value out of 10 attempts according to guidelines.[37] Two modes of IMT were tested in accordance with the manual supplied by the manufacturer, that is, inspiratory muscle strength training (IMST) with the resistance set to produce mouth pressures ≥80% of PI_{max} and inspiratory muscle endurance training (IMET) with the resistance set to produce mouth pressures at 60–80% of PI_{max}. In the IMST sessions, subjects performed five maximal inhalations repeated three times, separated by a 1-minute break. In the IMET sessions, subjects were instructed to breathe in and out 12–16 times for 1 minute, the frequency and power guided by an animation program ensuring correct pressures. Sequences of good technical quality were chosen for evaluation.

Evaluation of video recordings

The recordings were edited into new data files and reviewed in a random order by an experienced otolaryngologist (J-H.H.). Laryngeal movements were scored using a standardized system, modified from Maat et al.[38] (Figure 2). Laryngeal movements were graded from: maximal abduction (+2), moderate abduction (+1), neutral position (0), moderate adduction (−1), and severe adduction (−2). Laryngeal adduction has been reported to be a normal phenomenon at end-inspiration. Therefore, the inspiration was separated into three phases, the initial-, mid-, and end-inspiration, and only observations from the initial- and mid-inspiratory phases were tabulated.[39]

RESULTS

Mean age of the participants was 24 years (range 21–29 years); demographics outlined in Table 1. Spirometry confirmed normal lung function in all participants. All 20 volunteers, eight males and 12 females, successfully completed all examinations. PI_{max}, was normal in all subjects, that is, >50 cm H_2O[40] (Table 1). A relatively large heterogeneity was observed for laryngeal anatomy, although within normal limits in all (Figure 3). Throughout resting respiratory cycles, the expected vocal fold abduction during inspiration and a slight adduction during expiration were observed in all.

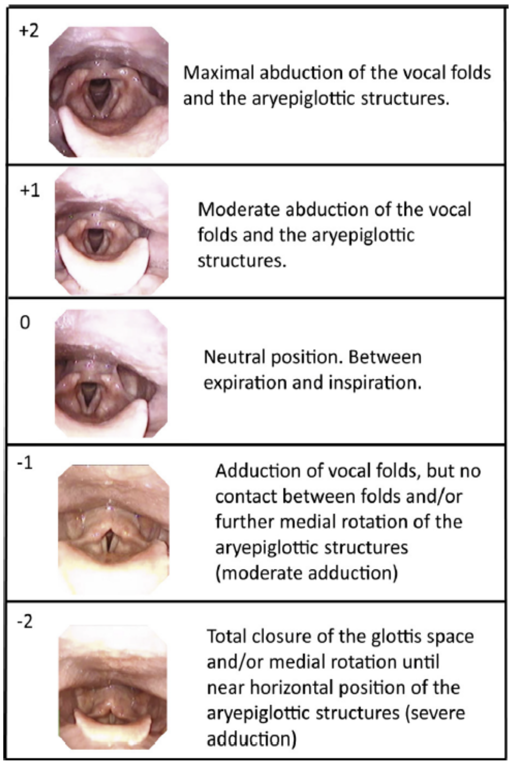


FIGURE 2. Scoring system.

Laryngeal response to IMT

The laryngeal response pattern to the muscular strength program (IMST) differed from that of the muscular endurance program (IMET). During the IMST program, a large variety of response patterns were observed (Figure 3). Visualization and evaluation of the vocal folds were disturbed by a juvenile epiglottis and severe hypopharyngeal constriction in one person. Hence, laryngeal scores could be obtained for 19 of the 20 participants (Table 2). Hypopharyngeal constriction to a less severe extent, still allowing for laryngeal evaluation, was seen in nine of the remaining 19 subjects. Six (32%) of the 19 subjects achieved maximal abduction of the laryngeal inlet throughout the complete inspiratory phase and another four (21%) subjects had a moderate abduction. Two of the four subjects with moderate abduction went from abduction in the initial phase to neutral position in the mid-inspiratory phase. In seven (37%) subjects, a neutral position was observed in the initial phase and six of these developed a moderate adduction in mid-inspiration. In the remaining two subjects, a moderate adduction was observed in the initial phase, one of whom developed a severe laryngeal adduction in mid-inspiration, initiated by the vocal folds (glottic level), and followed by aryepiglottic structures (supraglottic level). Laryngeal adduction was observed at end-inspiration in 13 (68%) subjects.

During the IMET program, hypopharyngeal constriction was observed in two of the 20 subjects, allowing for laryngeal evaluation in both. Laryngeal abduction in the initial- and mid-inspiratory phases was observed in 18 (90%) of the 20 subjects. In the remaining two (10%) subjects, the larynx initially adopted a neutral position, followed by a moderate adduction in mid-inspiration in one of them.

DISCUSSION

This is the first study to report direct visualization of laryngeal responses to IMT. Opening of the laryngeal aperture was demonstrated in 18 of 20 subjects when applying the settings of IMET and in 10 of 19 subjects when applying the settings of IMST. With IMST, the larynx of the remaining nine subjects adopted a neutral or adducted position already from the start of inspiration. In two of these, severe adduction was observed in mid-inspiration, almost completely obstructing the laryngeal inlet.

This study shows that video-recorded transnasal fiberoptic laryngoscopy is possible, feasible, and well tolerated during IMT in healthy subjects. The laryngeal movements were described according to a strict and preset system, and video recordings from the examinations can be replayed for later evaluation.[41] The IMT device was a targeted inspiratory resistive trainer, with two program options; muscular strength and muscular endurance. There are several IMT devices on the market, most not programmable, and our conclusions may not be transferrable to other devices. The age distribution of the study sample (21–29 years) may be considered a weakness of the study in relation to patients suffering from EILO.[4] EILO mainly concerns adolescents and the majority being females.[1,3,4] Because of the shape of the aryepiglottic folds and the cuneiform tubercles, the supraglottic space is relatively more narrow in teenagers than in adults. Moreover, the laryngeal structures become more rigid with age.[42,43] A significant sex difference regarding laryngeal dimensions has also been observed throughout the pubertal growth spurt.[43,44] A younger

TABLE 1.
Baseline Characteristics (n = 20)

	Age	BMI, kg/m^2	FVC, % of Predicted	FEV$_1$% of Predicted	PEF, % of Predicted	PI$_{max}$, cm H_2O	PE$_{max}$, cm H_2O	MV L/min
Mean	24.4	22.6	106.7	99.1	102.2	105.3	132.6	16.2
SD	1.9	2.0	8.5	13.0	15.6	27.9	28.3	3.5

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; MV, minute volume; PCF, peak cough flow; PEF, peak expiratory flow; PE$_{max}$, maximal expiratory mouth pressure; PI$_{max}$, maximal inspiratory mouth pressure; SD, standard deviation.

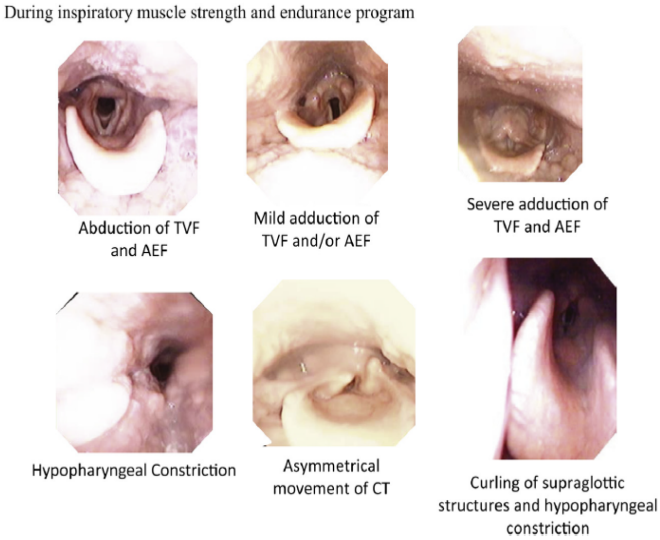


FIGURE 3. Examples of laryngeal response patterns during maximal IMT according to applied pressures and instructions. TVF, true vocal fold; AEF, aryepiglottic fold; CT, cuneiform tubercle.

study population, with an age distribution more representative for patients with EILO, might have produced even more heterogenous findings.

The ultimate goal of IMT in an EILO setting is to promote patency or preferably increase the size of the laryngeal inlet during conditions of vastly increased airflow during intense

TABLE 2.
Laryngeal Scoring to Maximal (Strength) and Moderate (Endurance) IMT

	IMT					
	Strength			Endurance		
Subjects	Initial*	Middle*	Hypopharyngeal Constriction	Initial*	Middle*	Hypopharyngeal Constriction
1	+2	+2	−2	+2	+2	0
2	+1	+1	0	+1	+1	0
3	0	−1	−1	+1	+1	0
4	+1	0	−1	+2	+2	0
5	+2	+2	−2	+2	+2	0
6	+2	+2	−2	+2	+2	−1
7	+2	+2	−1	+2	+2	0
8	+1	+1	0	+1	+1	0
9	+2	+2	−1	+2	+2	0
10	−1	−2	0	0	−1	0
11	0	−1	0	+1	+1	0
12	+2	+2	0	+1	+1	0
13	+1	0	0	+1	+1	0
14	0	−1	0	+1	+1	0
15	0	−1	0	0	0	0
16	−1	−1	−2	+1	+1	−2
17	0	−1	0	+1	+1	0
18	x	x	−2	+1	+1	0
19	0	−1	0	+1	+1	0
20	0	0	−2	+2	+2	0

Abbreviations: X, true vocal folds not visual; +2, maximal abduction; +1, moderate abduction; 0, resting position; −1, moderate adduction; −2, maximal adduction.
* Initial and middle refers to the respective phases of the inspiration.

physical exercise.[45] In accordance with the principle by Bernoulli, increased airflow velocity through the laryngeal orifice leads to increasing negative pressures inside the laryngeal lumen and therefore to an increasing inward pressure on the laryngeal structures.[46] These inward pressures are further increased with turbulent airflow. The larynx is protected from inspiratory collapse by a relatively rigid cartilage skeleton and by muscular actions, particularly from the PCA muscle, which is central in keeping the laryngeal inlet open during exercise. A possible fatigue of the PCA muscle over time has been suggested as an explanation for the collapse of laryngeal structures observed with EILO.[20,39,47–52]

Findings in the healthy subjects support existing knowledge of abduction of the vocal folds during inspiration and a slight adduction of the vocal cords during expiration. The resistance to airflow through the larynx is regulated mainly at the level of the vocal folds.[32] Vocal fold movements are accomplished by rotation and anterior-posterior sliding of the arytenoid cartilages. Medial rotation brings the vocal folds together in the midline in a lower position, thereby narrowing or closing the glottic airway. Rotation of the arytenoids laterally and abducting the vocal folds in an upper position are accomplished by a single pair of intrinsic muscles, the main abductor of the larynx, the PCA.[32] The respiratory movements of the vocal folds are closely coordinated with those of the diaphragm. During inspiration, increased activity of the PCA muscle occurs slightly before the diaphragm contracts and continues to mid-inspiration.[33,39] This increased activity of the PCA muscle increases the size of the opening of the laryngeal inlet and thereby reduces the airflow resistance. This is further reduced by contraction of the cricothyroid muscle, which leads to an anterior tilt of the thyroid cartilage relative to the cricoid, increasing the anterior-posterior dimension of the glottis, tensing the vocal folds, and increasing the glottic aperture.[34]

There are a few case reports in the literature reporting on responses from IMT in patients with laryngeal obstruction during exercise, but objective outcome measures have not been applied.[25–27] Healthy athletes have been reported to improve their exercise performance following IMT,[31] and IMT has also been used in the treatment of a wide range of diseases with different etiology.[26,29] In these studies, the inspiratory muscle strength and endurance has generally been improved by the IMT, but the clinical relevance is still uncertain.[28,53] The scientific evidence does not support the routine use of IMT as an essential component of pulmonary rehabilitation.[29] Why some patients respond well to IMT and others have no effect still remains to study. One may speculate if the varying effect from IMT could be related to the varying laryngeal responses to IMT observed in the healthy subjects of the present study, that is, that patients who do not have effect may be unable to engage the targeted muscle groups.

The diverse laryngeal response patterns observed in the present study underline the complexity of the larynx, with muscles working together in a complex and coordinated way. Laryngeal movements are consequences of concerted actions from groups of muscles, and training of one selected muscle such as the PCA may not be feasible. Therefore, to enhance laryngeal abduction, one must aim at engaging this muscular interaction. Based on our results, a desirable response and effect of IMT seems more dependent on the existence of a well-coordinated inspiratory motion than the power with which the training is performed. It seems that training at lower intensities may be superior to maximal strength training.

CONCLUSION

IMT can produce laryngeal abduction in healthy subjects, and the application of medium intensity resistance seems superior to higher resistance, which may be counterproductive. The findings are encouraging in terms of IMT being a treatment option for EILO. Large interindividual variability suggests a need for individualized and tailored treatment strategies, and randomized trials should be performed to evaluate the clinical effects of IMT.

REFERENCES

1. Christensen PM, Thomsen SF, Rasmussen N, Backer V. Exercise-induced laryngeal obstructions: prevalence and symptoms in the general public. *Eur Arch Otorhinolaryngol*. 2011;268:1313–1319.
2. Rundell KW, Spiering BA. Inspiratory stridor in elite athletes. *Chest*. 2003; 123:468–474.
3. Christopher KL, Morris MJ. Vocal cord dysfunction, paradoxic vocal fold motion, or laryngomalacia? Our understanding requires an interdisciplinary approach. *Otolaryngol Clin North Am*. 2010;43:43–66. viii.
4. Roksund OD, Maat RC, Heimdal JH, et al. Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. *Respir Med*. 2009;103: 1911–1918.
5. Christopher KL, Wood RP, Eckert RC, et al. Vocal-cord dysfunction presenting as asthma. *N Engl J Med*. 1983;308:1566–1570.
6. Andrianopoulos MV, Gallivan GJ, Gallivan KH. PVCM, PVCD, EPL, and irritable larynx syndrome: what are we talking about and how do we treat it? *J Voice*. 2000;14:607–618.
7. Kayani S, Shannon DC. Vocal cord dysfunction associated with exercise in adolescent girls. *Chest*. 1998;113:540–542.
8. Landwehr LP, Wood RP, Blager FB, Milgrom H. Vocal cord dysfunction mimicking exercise-induced bronchospasm in adolescents. *Pediatrics*. 1996;98:971–974.
9. Maturo S, Hill C, Bunting G, et al. Pediatric paradoxical vocal-fold motion: presentation and natural history. *Pediatrics*. 2011;128:e1443–e1449.
10. McFadden ER Jr, Zawadski DK. Vocal cord dysfunction masquerading as exercise-induced asthma. A physiologic cause for "choking" during athletic activities. *Am J Respir Crit Care Med*. 1996;153:942–947.
11. Morris MJ, Deal LE, Bean DR, et al. Vocal cord dysfunction in patients with exertional dyspnea. *Chest*. 1999;116:1676–1682.
12. Newsham KR, Klaben BK, Miller VJ, Saunders JE. Paradoxical vocal-cord dysfunction: management in athletes. *J Athl Train*. 2002;37:325–328.
13. Sullivan MD, Heywood BM, Beukelman DR. A treatment for vocal cord dysfunction in female athletes: an outcome study. *Laryngoscope*. 2001; 111:1751–1755.
14. Morrison M, Rammage L, Emami AJ. The irritable larynx syndrome. *J Voice*. 1999;13:447–455.
15. Brugman S. What's this thing called vocal cord dysfunction? Chest online. 2009. www.chestnet.org/education/online/pccu/vol20/lessons25-27/print26.php.
16. Smith MS. Acute psychogenic stridor in an adolescent athlete treated with hypnosis. *Pediatrics*. 1983;72:247–248.
17. Earles J, Kerr B, Kellar M. Psychophysiologic treatment of vocal cord dysfunction. *Ann Allergy Asthma Immunol*. 2003;90:669–671.
18. Rhodes RK. Diagnosing vocal cord dysfunction in young athletes. *J Am Acad Nurse Pract*. 2008;20:608–613.
19. Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics*. 2007;120:855–864.

20. Bent JP III, Miller DA, Kim JW, et al. Pediatric exercise-induced laryngomalacia. *Ann Otol Rhinol Laryngol*. 1996;105:169–175.
21. Maat RC, Roksund OD, Olofsson J, et al. Surgical treatment of exercise-induced laryngeal dysfunction. *Eur Arch Otorhinolaryngol*. 2007;264: 401–407.
22. Mandell DL, Arjmand EM. Laryngomalacia induced by exercise in a pediatric patient. *Int J Pediatr Otorhinolaryngol*. 2003;67: 999–1003.
23. McClurg FL, Evans DA. Laser laryngoplasty for laryngomalacia. *Laryngoscope*. 1994;104:247–252.
24. Smith RJ, Bauman NM, Bent JP, et al. Exercise-induced laryngomalacia. *Ann Otol Rhinol Laryngol*. 1995;104:537–541.
25. Baker SE, Sapienza CM, Martin D, et al. Inspiratory pressure threshold training for upper airway limitation: a case of bilateral abductor vocal fold paralysis. *J Voice*. 2003;17:384–394.
26. Mathers-Schmidt BA, Brilla LR. Inspiratory muscle training in exercise-induced paradoxical vocal fold motion. *J Voice*. 2005;19: 635–644.
27. Ruddy BH, Davenport P, Baylor J, et al. Inspiratory muscle strength training with behavioral therapy in a case of a rower with presumed exercise-induced paradoxical vocal-fold dysfunction. *Int J Pediatr Otorhinolaryngol*. 2004;68:1327–1332.
28. Gosselink R, De VJ, van den Heuvel SP, et al. Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J*. 2011; 37:416–425.
29. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest*. 2007;131:4S–42S.
30. Forbes S, Game A, Syrotuik D, et al. The effect of inspiratory and expiratory respiratory muscle training in rowers. *Res Sports Med*. 2011;19: 217–230.
31. Illi SK, Held U, Frank I, Spengler CM. Effect of respiratory muscle training on exercise performance in healthy individuals: a systematic review and meta-analysis. *Sports Med*. 2012;42:707–724.
32. Barlett D Jr. Respiratory functions of the larynx. *Physiol Rev*. 1989;69: 33–51.
33. Brancatisano TP, Dodd DS, Engel LA. Respiratory activity of posterior cricoarytenoid muscle and vocal cords in humans. *J Appl Physiol*. 1984;57: 1143–1149.
34. Petcu LG, Sasaki CT. Laryngeal anatomy and physiology. *Clin Chest Med*. 1991;12:415–423.
35. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993;16: 5–40.
36. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis*. 1983;127:725–734.
37. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med*. 2002;166:518–624.
38. Maat RC, Roksund OD, Halvorsen T, et al. Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations. *Eur Arch Otorhinolaryngol*. 2009;266:1929–1936.
39. Kuna ST, Vanoye CR. Laryngeal response during forced vital capacity maneuvers in normal adult humans. *Am J Respir Crit Care Med*. 1994;150: 729–734.
40. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in Caucasian adults and children. *Thorax*. 1984;39:535–538.
41. Heimdal JH, Roksund OD, Halvorsen T, et al. Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise. *Laryngoscope*. 2006;116:52–57.
42. Fried MP. *The Larynx. A Multidisciplinary Approach*. 2rd ed. St. Louis, MO: Mosby; 1996. 18–45.
43. Wysocki J, Kielska E, Orszulak P, Reymond J. Measurements of pre- and postpubertal human larynx: a cadaver study. *Surg Radiol Anat*. 2008;30: 191–199.
44. Castelli WA, Ramirez PC, Nasjleti CE. Linear growth study of the pharyngeal cavity. *J Dent Res*. 1973;52:1245–1248.
45. Eichenwald EC, Stark AR. High-frequency ventilation: current status. *Pediatr Rev*. 1999;20:e127–e133.
46. Fajdiga I. Snoring imaging: could Bernoulli explain it all? *Chest*. 2005;128: 896–901.
47. Baier H, Wanner A, Zarzecki S, Sackner MA. Relationships among glottis opening, respiratory flow, and upper airway resistance in humans. *J Appl Physiol*. 1977;43:603–611.
48. Belmont JR, Grundfast K. Congenital laryngeal stridor (laryngomalacia): etiologic factors and associated disorders. *Ann Otol Rhinol Laryngol*. 1984;93:430–437.
49. Brancatisano T, Collett PW, Engel LA. Respiratory movements of the vocal cords. *J Appl Physiol*. 1983;54:1269–1276.
50. Cole P, Savard P, Miljeteig H, Haight JS. Resistance to respiratory airflow of the extrapulmonary airways. *Laryngoscope*. 1993;103:447–450.
51. Fink BR, Basek M, Epanchin V. The mechanism of opening of the human larynx. *Laryngoscope*. 1956;66:410–425.
52. Hurbis CG, Schild JA. Laryngeal changes during exercise and exercise-induced asthma. *Ann Otol Rhinol Laryngol*. 1991;100:34–37.
53. Geddes EL, O'Brien K, Reid WD, et al. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respir Med*. 2008;102:1715–1729.

Open access Original article

BMJ Open Sport & Exercise Medicine

Exercise-induced laryngeal obstruction in athletes treated with inspiratory muscle training

Astrid Sandnes,[1,2] Tiina Andersen,[2,3,4] Hege Havstad Clemm,[2,5] Magnus Hilland,[6] Maria Vollsæter,[2,3,5] John-Helge Heimdal,[6,7,8] Geir Egil Eide,[9,10] Thomas Halvorsen,[2,5] Ola Drange Røksund[4,5,11]

To cite: Sandnes A, Andersen T, Clemm HH, *et al*. Exercise-induced laryngeal obstruction in athletes treated with inspiratory muscle training. *BMJ Open Sport & Exercise Medicine* 2019;**5**:e000436. doi:10.1136/bmjsem-2018-000436

Accepted 18 December 2018

For numbered affiliations see end of article.

Correspondence to
Dr Astrid Sandnes; astrid.sandnes@sykehuset-innlandet.no

ABSTRACT

Background Exercise-induced laryngeal obstruction (EILO) is common in athletes and presents with dyspnoea, chest tightness, inspiratory stridor and sometimes panic reactions. The evidence for conservative treatment is weak, but case reports suggest effects from inspiratory muscle training (IMT). We aimed to explore effects from IMT used in athletes with EILO.

Method Twenty-eight athletes, mean age 16.4 years, diagnosed with EILO at our clinic, participated in a 6-week treatment programme, using a resistive flow-dependent IMT device (Respifit S). Four athletes competed at international level, 13 at national and 11 at regional levels. Video-recorded continuous transnasal flexible laryngoscopy was performed from rest to peak exercise (continuous laryngoscopy exercise (CLE) test) and scored before and 2–4 weeks after the training period. Ergospirometric variables were obtained from this CLE set-up. Lung function was measured according to guidelines. Symptom scores and demographic variables were obtained from a questionnaire.

Results After the treatment period, symptoms had decreased in 22/28 (79%) participants. Mean overall CLE score had improved after treatment ($p<0.001$), with the scores becoming normal in five athletes but worse in two. Most of the improvement was explained by changes at the glottic laryngeal level ($p=0.009$). Ergospirometric variables revealed significantly higher peak minute ventilation explained by higher tidal volumes and were otherwise unchanged.

Conclusion This explorative study underlines the heterogeneous treatment response of EILO and suggests that IMT may become an efficient conservative treatment tool in subgroups, possibly contributing to better control of the vocal folds. The signals from this study should be tested in future controlled interventional studies.

What are the new findings?

- This explorative study of athletes with exercise-induced laryngeal obstruction (EILO) suggests that respiratory symptoms and scores from continuous laryngoscopy exercise (CLE) tests can improve after a treatment period with inspiratory muscle training (IMT).
- The IMT treatment period primarily seemed to improve the glottic CLE subscores.
- IMT may be a tool to treat subgroups of athletes with EILO; however, controlled trials are needed to establish the scientific evidence.

How might it impact on clinical practice in the future?

- The findings further substantiate that larynx should be visualised from rest to peak exertion in all athletes who suffer from symptoms suggesting EILO.
- The findings highlight the heterogeneity of EILO, and that future treatment is likely to be individually tailored and based on a more comprehensive phenotyping than today.
- The study provides data that can serve as basis for setting up controlled studies on IMT used to treat EILO in athletes.
- Providing the findings are verified in future controlled studies, IMT may become a conservative treatment tool for subgroups of EILO, possibly contributing to better control of the vocal fold movements.

INTRODUCTION

Exercise-induced inspiratory symptoms (EIIS) are common in young athletes,[1] and primarily characterised by prolonged and/or noisy inspiration and shortness of breath.[2] EIIS usually occurs during vigorous exercise when the ventilation requirement is high and resolves spontaneously shortly after termination of the exertion. EIIS are most often related to obstruction of the larynx, involving either supraglottic laryngeal structures and/or the vocal folds, and should then be labelled exercise-induced laryngeal obstruction (EILO).[3 4] The prevalence of EILO in unselected young Scandinavian populations has been reported to be 5.7% and 7.5%,[5 6] and as high as 35.2% in athletes.[1]

Despite widely different pathophysiology, EILO is often confused with exercise-induced bronchoconstriction (EIB) which is an unfortunate situation that sometimes leads to prescription of high doses of asthma medication.[1 2 6–9] The literature highlights that EILO should be diagnosed by means of objective methodology, visualising the laryngeal structures from rest to peak exertion.[3] In most cases, the obstruction seems to originate in supraglottic structures (including the epiglottis) during the inspiratory phase of the breathing cycles, increasing as the ventilatory requirements increase with increasing exercise load,[9 10] before glottic structures become involved, seemingly as a secondary phenomenon; however, this is not always so.[2 11 12] This observed heterogeneity in the laryngeal findings suggests that *one* treatment modality is unlikely to work in *all* phenotypes of EILO.

So far, the evidence base for EILO treatment has been weak, generally consisting of small studies or single case reports conducted in poorly defined patient groups (EILO phenotypes), often with vaguely defined outcome measures.[4] Historically, there are case reports suggesting effects from inspiratory muscle training (IMT).[12–15] However, the mechanisms involved are unclear, for example, we do not know if IMT would influence glottic and supraglottic EILO in different ways, information that would aid the planning of further studies of this treatment. Thus, aiming to expand our knowledge on non-invasive treatment tools for EILO, we embarked on this explorative study, addressing effects from IMT offered to motivated athletes consecutively presenting at our EILO clinic, irrespective of phenotype.

METHODS

Participants and study design

Within an explorative study design, all athletes consecutively referred for work-up of EIIS and diagnosed with EILO at the outpatient clinic at the Pediatric Department of Haukeland University Hospital in Western Norway between May 2012 and May 2014 were offered a structured treatment period with IMT, providing a device was available (ie, convenience-based inclusion within a given time frame). The inclusion criteria required that the severity scores of EILO obtained during a continuous laryngoscopy exercise (CLE) test[16] were graded as two or more, either at the supraglottic level or at the vocal folds (ie, the glottic level)[17] (regarding CLE scores, see figure 1). Moreover, there should be no evidence that EIB could explain the patient's symptoms. Asthma per se was not an exclusion criterion, but in cases where asthma was present or suspected, EIB was excluded as cause of symptoms by performing a standardised test as described by Carlsen *et al*, either at our institution or by the referring institution.[18] CLE scores, lung function and ergospirometry data were collected before and 2–4 weeks after the IMT treatment period, as were symptom scores obtained using a standardised questionnaire that also served to obtain demographic background variables. All athletes answered the question "*When you are physically active, how much are you bothered by your breathing difficulties?*", using a numeric rating scale from 1 to 5 (1=nothing, 2=a bit, 3=pretty much, 4=a lot and 5=disabling). The study was approved by the Committee on Medical Research Ethics of Western Norway (REK number 2009/2111), and informed written consent was obtained from the participants.

CLE test

An integrated set-up for continuous video-recorded laryngoscopy throughout a maximal cardiopulmonary exercise test, coupled with video recordings of the upper part of the body and sound recordings, was applied as previously described.[16]

A transnasal flexible fiberoptic laryngoscope (Olympus ENF-P3, Tokyo, Japan), diameter 3.5 mm, was introduced after applying a decongestive nasal spray (Rhinox) and local anaesthesia (Xylocaine), and secured in a position allowing for a good view of the laryngeal entrance, including both supraglottic structures and the vocal folds. Continuous video recordings from the laryngoscope, a film of the upper part of the body and breath sounds were obtained simultaneously throughout the exercise test and stored in one single file for later evaluation. Laryngeal movements were scored as described previously[17]; at moderate (ie, when the test person changed from walking to running) and at maximal exercise intensity at glottic (labelled A and C, respectively) and supraglottic (labelled B and D, respectively) levels, and additionally a total sum score labelled E (figure 1). A CLE subscore of 1 (glottic or supraglottic) was regarded as normal.[2] All assessments were done by two experienced raters (HHC and ODR) who were exposed to anonymised video recordings from all participants, blinded to the circumstances under which the video had been obtained, that is, if the video had been obtained before or after the treatment period. An uninvolved photographer presented the two films from each participant in random order. Disagreements were solved by consensus. Clinical symptoms during the CLE test were recorded in a questionnaire.

Pulmonary function and exercise test

Spirometry was performed with a Vmax 22 (SensorMedics, Yorba Linda, California, USA) according to guidelines,[19] recording FVC, FEV_1 and forced expiratory flow at 50% of FVC ($FEF_{50\%}$), and reported as percentages of predicted.[20] Forced inspiratory volume in first second (FIV_1) and forced inspiratory flow at 50% ($FIF_{50\%}$) of forced inspiratory volume capacity were recorded, and FEF_{50}/FIF_{50} and FEV_1/FIV_1 were calculated and classified as abnormal if exceeding 1.5.[8] The configuration of the flow-volume loops (FVL) was classified as normal or abnormal by an experienced respiratory physiologist (ODR), based on flattening or truncation of the inspiratory limbs.[21] The patients ran on a treadmill (Woodway ELG 70, Weil am Rhein, Germany) using a computerised and modified Bruce protocol,[22] increasing speed and/or elevation every minute, aiming to reach maximum exercise capacity after 6–12 min. Variables of gas exchange were measured breath by breath using a facemask (Hans

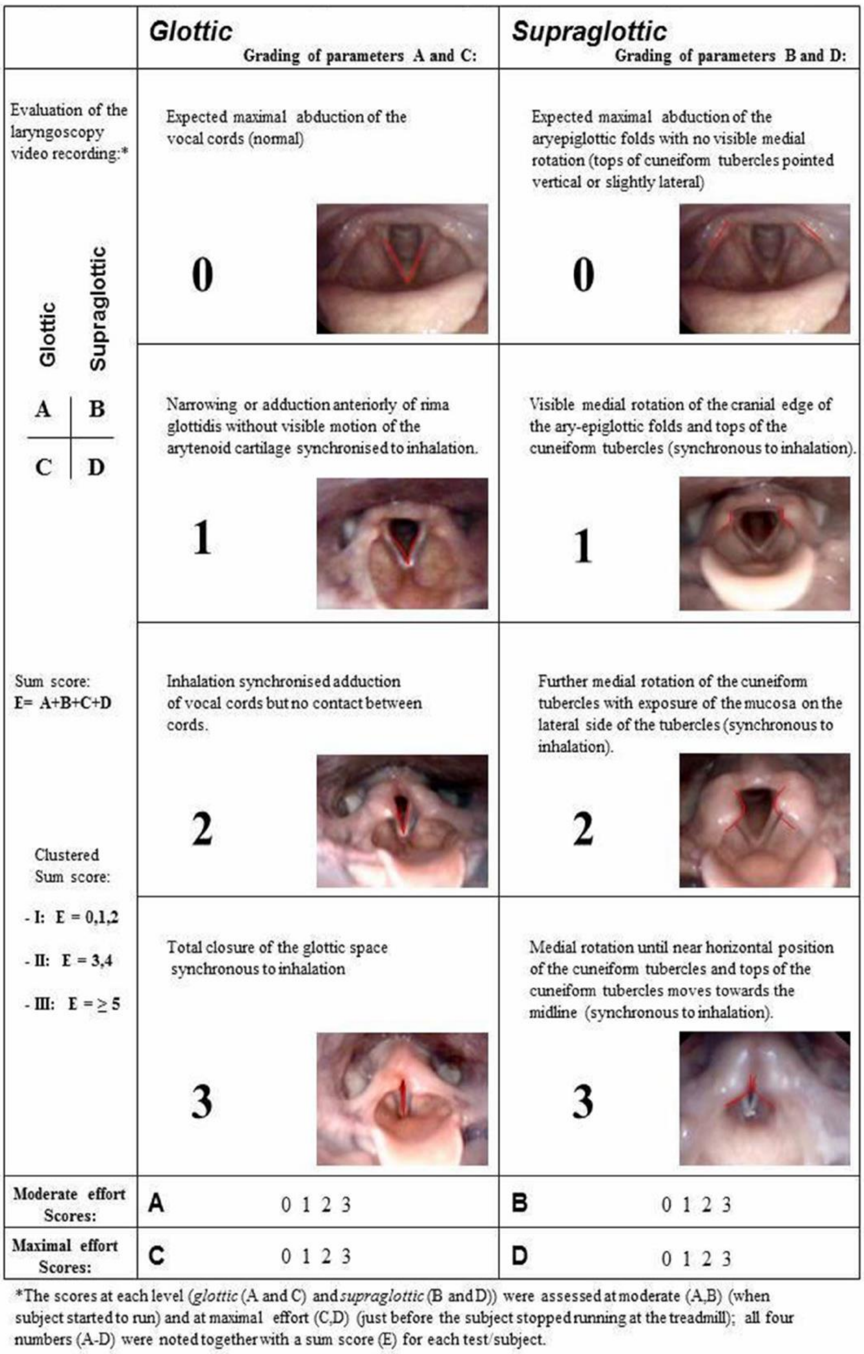


Figure 1 Grading system according to Maat *et al*[17] reproduced with permission.

Rudolph, Kansas City, Missouri, USA) connected to a Jaeger Oxycon Pro Cardiopulmonary Exercise testing system (Viasys Health Care, Yorba Linda, California, USA). The test was considered successful if the patient continued until exhaustion, preferably supported by a plateau in oxygen consumption and/or the heart rate response, or until stopped by respiratory distress. Duration and distance on treadmill running were recorded.

Inspiratory muscle training

Respifit S (Biegler GmbH, Mauerbach, Austria) was used to measure the maximal inspiratory mouth pressure (PI_{max}), using the best value of 10 according to guidelines[23] in order to provide exact settings of the resistance during the IMT sessions. The same device was used for the 6-week training sessions. To promote correct breathing technique, the participants were instructed to inhale using the diaphragm and to minimise movements of the shoulders in the cranial direction. Two modes of inspiratory muscle training were tested in accordance with the manual supplied by the manufacturer, that is, (1) inspiratory muscle strength training (IMST) with the resistance set to produce mouth pressures ≥80% of PI_{max} and (2) moderate resistance or inspiratory muscle endurance training (IMET) with the resistance set at 60%–80% of PI_{max}. In the IMST sessions, subjects performed five maximal inhalations repeated three times, separated by a 1 min break. In the IMET sessions, subjects were instructed to breathe in and out 12–16 times for 1 min. The frequency and power were guided by an animation program ensuring correct use of the device, and data from each training session were stored by a memory card measuring treatment compliance. The participants trained every day, in cycles of 2 days with IMET followed by 1 day of IMST, for a total of 6 weeks.

Statistical methods

This was a descriptive study, with main outcomes being the CLE scores and symptom scores obtained before versus after the IMT treatment period, compared using Gosset's paired sample t-test.[24] Means, SD, 95% CIs and ranges were calculated, as appropriate. The CLE scores are by nature ordinal and categorical, ranging from 0 to 3. Due to the few number of categories, the data were reported as mean values and mean differences with 95% CI, as this is considered to provide more information than medians and IQRs.[25] Mixed linear model regression including interaction terms were applied to address if CLE-score changes (before vs after the treatment period) differed when obtained at moderate versus maximal exercise intensity and at the glottic versus supraglottic laryngeal level.[26]

All analyses were performed with SPSS V.24.

RESULTS

Fifty-one eligible athletes presented to our clinic during the inclusion period, of whom 30 (59%) were included within the convenience-based sampling structure of the study. Two included athletes had to be excluded due to incomplete data sets. The age range of the remaining 28 was 12–25 years (mean 16.4), 4 males and 24 females. Four athletes were competing at international level, 13 at a national level and 11 at a regional level, and they were engaged in various endurance sports (table 1). Lung function was normal in all.

Subjective scores

After the IMT treatment period, 22/28 (79%) responded yes to a question if they felt their EILO problem had improved during the treatment period. Mean (SD) ratings obtained before versus after the IMT treatment period to the question "*how much are you bothered by your breathing difficulties*" were 3.63 (0.79) versus 2.93 (1.07), respectively (p<0.001). After the IMT treatment period, 12/28 (43%) athletes responded *nothing* or *a bit* to this question, whereas one reported that symptoms had increased.

Table 1 Characteristics of 28 included athletes consecutively referred for work-up of EIIS and diagnosed with EILO at the outpatient clinic at the Pediatric Department of Haukeland University Hospital in Bergen, Norway between May 2012 and May 2014 who were offered a structured treatment period with IMT

Variable	N=28
Category	**Statistic**
Female, n (%)	24 (85.7)
Age in years, mean (SD)	16.4 (2.8)
Height in cm, mean (SD)	169.4 (8.4)
Weight in kg, mean (SD)	61.6 (10.9)
Type of sports, n	
Soccer	6
Handball	6
Cross-country skiing	4
Biathlon	4
Athletics	2
Cycling	2
Swimming	2
Running	1
Kayaking	1
Competition level, n	
International	4
National	13
National regional	11
Level of laryngeal obstruction*	
Supraglottic>glottic	7/28
Glottic>supraglottic	2/28
Supraglottic=glottic	19/28
Solely glottic	0/28

*At maximum exercise, before IMT.
EIIS, exercise-induced inspiratory symptom; EILO, exercise-induced laryngeal obstruction; IMT, inspiratory muscle training.

Laryngeal findings during exercise (CLE scores)

At diagnosis, before the treatment period at maximum exercise, none had a solely glottic obstruction, 7/28 had supraglottic score exceeding the glottic score, 2/28 had glottic score exceeding the supraglottic score and 19/28 had similar supraglottic and glottic score (table 1). After the IMT treatment period, 5/28 (18%) athletes had no signs of laryngeal obstruction, presenting with CLE sum scores 0 or 1. In 23/28 (82%) athletes, the CLE sum scores had improved, eight of whom had a decrease in CLE sum score of two or more, whereas 3/28 had the same CLE

Table 2 Mean CLE score differences as obtained at glottic and supraglottic laryngeal levels at moderate and maximal exercise intensity before versus after the IMT treatment period in 28 included athletes consecutively referred for work-up of EIIS and diagnosed with EILO at the outpatient clinic at the Pediatric Department of Haukeland University Hospital in Bergen, Norway between May 2012 and May 2014 as estimated from mixed model linear regression analysis

Exercise intensity	Glottic/supraglottic	CLE score differences	SE	95% CI	F-test p value*
Moderate	Glottic	0.11	0.13	−0.16 to 0.37	0.426
Moderate	Supraglottic	0.07	0.13	−0.19 to 0.34	0.596
Maximal	Glottic	0.93	0.13	0.66 to 1.19	<0.001
Maximal	Supraglottic	0.18	0.13	−0.09 to 0.44	0.186
Overall		0.32	0.07	0.19 to 0.54	<0.001

*P value for three-way interaction: 0.009.
CLE, continuous laryngoscopy exercise; EIIS, exercise-induced inspiratory symptom; EILO, exercise-induced laryngeal obstruction; IMT, inspiratory muscle training.

sum scores before and after the treatment period. In two athletes, the CLE sum score had increased, of whom one was judged by both raters as a classical supraglottic phenotype of EILO and the other as a typical glottic EILO phenotype, characterised by anxiety and panic.

The pre-treatment versus the post-treatment differences in the CLE scores are given in table 2. A significant difference was observed only at maximal exercise intensity at the glottic laryngeal level. In the mixed model linear regression of CLE scores obtained pre-treatment versus post-treatment at moderate versus maximal exercise intensity at the glottic versus the supraglottic laryngeal level, the three-way interaction was found to be highly significant (F-test p=0.009) (table 2), confirming that CLE-score changes at maximal exercise intensity at the glottic laryngeal level explained most of the overall effect. The mean CLE scores with 95% CIs are presented in figure 2.

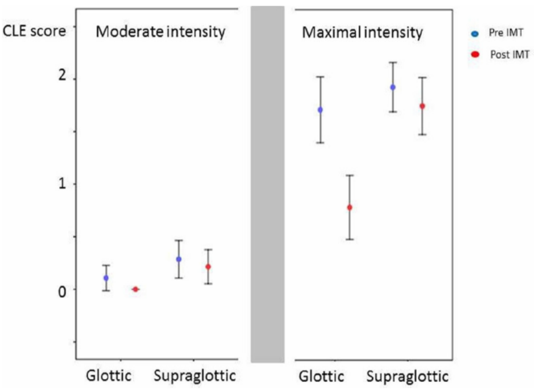


Figure 2 CLE scores before and after treatment with IMT of 28 athletes consecutively referred for work-up of EIIS and diagnosed with EILO at the outpatient clinic at the Pediatric Department of Haukeland University Hospital in Bergen, Norway between May 2012 and May 2014. Dots represent mean values, and vertical lines represent 95% confidence intervals. CLE-scores, Continuous laryngoscopy exercise test (0-3); IMT, Inspiratory Muscle training; EIIS, Exercise induced inspiratory symptoms; EILO, Exercise induced laryngeal obstruction.

Spirometric and cardiopulmonary outcomes

The shape of the inspiratory limb of the flow-volume loop could be assessed in 25/28 athletes. The configuration was deemed abnormal in 5/28 (17.9%); however, FEF_{50}/FIF_{50} and FEV_1/FIV ratios exceeding 1.5 were not seen in any. Still, the FEF_{50}/FIF_{50} ratio was significantly lower after versus before the IMT treatment period (table 3).

The distance completed, the time spent running on the treadmill, the obtained peak VO_2 and the maximal heart rate did not differ before versus after the IMT treatment period. The minute ventilation (VE) and the tidal volume (Vt) increased significantly during the IMT training period, and the breathing rate was numerically (although not significantly) slightly reduced (table 3).

DISCUSSION

After a 6-week training period with IMT, most participating athletes (22/28 or 79%) reported subjective improvement. The CLE scores improved in 23 participants (82%), had become normal in five (18%) but worse in two (7%). Improvements were linked to a change at the glottic laryngeal level at peak exercise. Ergospirometric variables revealed significantly higher peak VE explained by higher Vt but were otherwise unchanged (eg, no changes in peak VO_2). The findings suggest that controlled studies should be incited, hypothesising that IMT can become an efficient treatment modality in subgroups of EILO, with particular focus on studying patients with glottic EILO.

Strengths and weaknesses of the study

The major strength of this study was the application of the best available and also a verifiable outcome measure, that is, CLE scores obtained before and after the IMT treatment period. CLE scores are based on endoscopic visual evaluation of laryngeal structures from rest to peak exercise, which is the gold standard for diagnosing EILO.[3] CLE testing has been successfully applied in

Table 3 Physiological outcomes in 28 included athletes consecutively referred for work-up of EIIS and diagnosed with EILO at the outpatient clinic at the Pediatric Department of Haukeland University Hospital in Bergen, Norway between May 2012 and May 2014

	Pre-IMT n=28	Post-IMT n=28	P value
PEF % predicted	105.6 (13.6)	108.0 (13.0)	0.020
FVC % predicted	111.9 (11.4)	112.2 (12.1)	0.685
FEV_1 % predicted	113.8 (11.0)	113.3 (10.5)	0.636
FEV_1/FIV_1	0.98 (0.1)	0.97 (0.1)	0.432
FEF_{50}/FIF_{50}	0.98 (0.2)	0.90 (0.2)	0.017
Distance on treadmill (m)	778.2 (159.8)	800.5 (174.7)	0.136
Time on treadmill (min)	10.9 (1.28)	11.0 (1.36)	0.248
Heart rate max (bpm)	187 (10)	187 (8)	0.853
VO_2 peak (mL/min)	3143 (654)	3135 (644)	0.856
VO_2 peak (mL/min/kg)	51.6 (9.2)	51.1 (8.9)	0.415
VE (L/min)	105.1 (26.0)	109.6 (24.2)	0.036
Breathing reserve (%)	17.5 (13.0)	14.2 (11.6)	0.057
Breathing rate (breaths/min)	50 (9)	48 (7)	0.224
Vt (L/breath)	2.14 (0.50)	2.31 (0.51)	0.003

EIIS, exercise-induced inspiratory symptom; EILO, exercise-induced laryngeal obstruction; FEF50, forced expiratory flow at 50%; FEV1, forced expiratory volume in first second; FIF50, forced inspiratory flow at 50%; FIV1, forced inspiratory volume in first second; IMT, inspiratory muscle training; PEF, peak expiratory flow; VE, Minute ventilation; VO2 peak, peak oxygen uptake; Vt, Tidal volume.

numerous recent studies in this field of respiratory medicine.[1 2 4–6 11 17 27–35] Studies addressing the validity and reliability of the CLE scoring system have reached somewhat variable conclusions.[17 36 37] It nevertheless seems reasonable to conclude that experience is a factor that influences these issues. In this study, two highly experienced raters, both having assessed CLE recordings form approximately 2000 patients, performed all scoring procedures according to a strict system designed to handle the expressed concerns to the extent possible. Previous studies addressing effects from treatments of EILO have mostly relied on symptom reports. As symptoms reported by patients with exercise-related breathing problems have been found inadequate as a diagnostic tool in several studies,[1 2 5 6 11 38 39] a similar inadequacy seems likely to expect also in a context addressing effects from treatments. Thus, in this respect, this study represents an improvement. The convenience-based sampling process with relatively few participants with a strong preponderance of young female participants are obvious weaknesses. There are no published well-designed epidemiological studies of EILO in athletes; however, most, but not all,[6] clinical studies report age and sex distributions similar to this present study.[2 5 40] Finally, the lack of a control group or some sort of 'sham treatment' clearly weakens the conclusions, as this leaves the study open for unknown effects from participants becoming familiarised with the CLE procedure, and thus might have become more relaxed at the second test performed after the treatment period. Having in mind the explorative study design, these weaknesses should incite designing properly controlled studies of IMT in EILO, focusing particularly on the glottic components.

Inspiratory muscle training

The theoretical basis for testing effects from IMT in patients suffering from EILO is based on the phasic relationship that exists between the diaphragm and the posterior cricoarytenoid (PCA) muscle, which is the main abductor of the vocal folds.[41 42] Signalled via the vagal nerve, the PCA muscle contracts slightly before the diaphragm, abducting the larynx before air starts entering the airways.[43] By using MRI, How *et al* demonstrated that also upper airway dilator muscles, external muscles as genioglossus and geniohyoid, are activated in response to IMT, providing evidence for IMT being able to condition upper airway muscles.[44] We have previously reported how various IMT modes influenced the larynx in healthy subjects, with lower resistance loads seemingly targeting abduction better than higher loads[30] suggesting that IMT applied as low-intensity endurance training (IMET) would be better suited as treatment for EILO than IMST. Since this present study was the first to apply IMT in a systematic way in patients with EILO, we nonetheless chose the training program prescribed by the manual provided by the manufacturer. Previous studies on other groups of patients have tended to use resistance load set from 40% to 90% of PI_{max}.[13 14 45 46] We need a randomised control study to solve this issue with IMST versus IMET.

The goal of any treatment for EILO is to achieve a more effective and better controlled laryngeal abduction during exercise, and thereby facilitate air flowing through the laryngeal inlet at an increasing speed without causing an undue increase of resistance. Our study showed a significant improvement in minute ventilation, necessarily reflecting also increased airflow through the larynx. This outcome was related to a significant increase in Vt and a tendency for lower breath rates (not significant); however, it was somewhat inconsistent from test to test and therefore difficult to interpret physiologically. Peak VO_2 did not differ, suggesting a relieved (improved) breathing pattern at peak exercise. Regrettably, we do not have access to blood gases to properly substantiate such potential ventilatory effects. Resting spirometry obtained before and after the treatment period confirmed low sensitivity in relation to diagnosing EILO,[47] but a significant decreased FEF_{50}/FIF_{50} ratio after treatment suggests that inspiratory resistance was reduced, also at rest.

CLE scores as outcome measure in EILO treatment studies

The evidence base for effects of different treatment options for EILO is limited, and a general lack of verifiable outcome measures complicates interpretations of previous studies. PI_{max} is the most commonly used IMT outcome measure, but in patients with EILO, PI_{max} seems irrelevant since the treatment targets coordination of inspiratory laryngeal movements more than the strength of the diaphragm.[30] Reports of subjective improvements certainly provide information that is important, but has serious sources of error,[48] and do not enhance our causal understanding. The use of verifiable visual laryngeal outcome measures such as CLE scores[16 17] can provide information that serve to understand this prevalent condition better, for example, contribute to distinguishing psychological from organic breathing problems, and to understand what structures incite and perpetuate the pathology of a malfunctioning larynx in a patient with EILO. Studies have questioned inter-rater reliability of CLE scores,[37] and measures should be taken to ensure a high level of experience among raters, with disagreements solved by consensus, as in this study. We have reported highly divergent responses to IMT in a previous case report,[12] further substantiated in this study with two participants deteriorating after the treatment period. Effects seemed linked to changes at the glottic level during maximum intensity suggesting that IMT may be most likely to improve EILO where glottic structures are most heavily involved. Moreover, one should probably be careful applying IMT in patients with a predominant supraglottic EILO. However, these are data revealed in an uncontrolled and explorative study, and we need well-designed in-depth controlled studies to investigate these signals further.

CONCLUSION

This study underlines the heterogeneity of EILO and suggests that future treatment is likely to be individually tailored and based on a more comprehensive phenotyping than today. The study suggests that IMT may become an efficient conservative treatment tool in subgroups of EILO, and that IMT might contribute to the patient achieving a better control of particularly the vocal fold movements. The signals from this explorative study should be tested in future controlled interventional studies. The cliche 'more studies are needed' certainly applies to this large and under-studied group of patients.

Author affiliations
[1]Department of Medicine, Innlandet Hospital Trust, Gjøvik, Norway
[2]Department of Clinical Science, University of Bergen, Bergen, Norway
[3]Thoracic Department, Norwegian Advisory Unit on Home Mechanical Ventilation, Bergen,
, Norway
[4]Department of Physiotherapy, Haukeland University Hospital, Bergen, Norway
[5]Department of Pediatrics, Haukeland University Hospital, Bergen, Norway
[6]Department of Otolaryngology/Head and Neck surgery, Haukeland University Hospital, Bergen, Norway
[7]Department of Surgery, Haukeland University Hospital, Bergen, Norway
[8]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[9]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway
[10]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[11]The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway

Acknowledgements Previously presented abstract and poster at the American Thoracic Society meeting in San Francisco, 2012.

Contributors AS: main author, substantial contributions to the conception of the work, data collection and drafting the manuscript. TA: substantial contributions to the conception of the work, critically revising the work and final approval of the version to be published. HHC: substantial contributions to the conception of the work, data collection, critically revising the work and final approval of the version to be published. MH: substantial contributions to critically revising the work and final approval of the version to be published. MV: substantial contributions to the conception of the work, data collection, critically revising the work and final approval of the version to be published. J-HH: substantial contributions to critically revising the work and interpretation of data, final approval of the version to be published. GEE: substantial contributions to statistical analysis and interpretation of the work, final approval of the version to be published. TH: substantial contributions to the conception or design of the work, interpretation of data and revising the manuscript, final approval of the version to be published. ODR: substantial contributions to the conception or design of the work, data collection, interpretation of data and revising the manuscript, final approval of the version to be published.

Funding Major funding institutions: Haukeland University Hospital and University of Bergen.

Competing interests Haukeland University Hospital owns parts of US patent No. 11/134551, protecting the commercial rights of the CLE test.

Patient consent for publication Obtained.

Ethics approval The study was approved by the Committee on Medical Research Ethics of Western Norway (REK no. 2009/2111).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Deidentified participant data such as ergospirometry data, questionnaire and images/film of the laryngeal obstruction are available by reasonable request to the main author.

REFERENCES

1. Nielsen EW, Hull JH, Backer V. High prevalence of exercise-induced laryngeal obstruction in athletes. *Med Sci Sports Exerc* 2013;45:2030–5.
2. Røksund OD, Maat RC, Heimdal JH, *et al*. Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. *Respir Med* 2009;103:1911–8.
3. Christensen PM, Heimdal J-H, Christopher KL, *et al*. ERS/ELS/ACCP 2013 international consensus conference nomenclature on inducible laryngeal obstructions: TABLE 1. *Eur Respir Rev* 2015;24:445–50.
4. Halvorsen T, Walsted ES, Bucca C, *et al*. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. *Eur Respir J* 2017;50:1602221.
5. Christensen PM, Thomsen SF, Rasmussen N, *et al*. Exercise-induced laryngeal obstructions: prevalence and symptoms in the general public. *Eur Arch Otorhinolaryngol* 2011;268:1313–9.
6. Johansson H, Norlander K, Berglund L, *et al*. Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. *Thorax* 2015;70:57–63.
7. Rice SG, Bierman CW, Shapiro GG, *et al*. Identification of exercise-induced asthma among intercollegiate athletes. *Ann Allergy* 1985;55:790–3.
8. Rundell KW, Spiering BA. Inspiratory stridor in elite athletes. *Chest* 2003;123:468–74.
9. Hull JH. Not all wheeze is asthma: time for patients to exercise their rights. *Thorax* 2015;70:7–8.
10. Christopher KL, Wood RP, Eckert RC, *et al*. Vocal-cord dysfunction presenting as asthma. *N Engl J Med* 1983;308:1566–70.
11. Buchvald F, Phillipsen LD, Hjuler T, *et al*. Exercise-induced inspiratory symptoms in school children. *Pediatr Pulmonol* 2016;51:1200–5.
12. Clemm HSH, Sandnes A, Vollsæter M. The heterogeneity of exercise-induced laryngeal obstruction. *Am J Respir Crit Care Med* 2018;197:1068–9.
13. Ruddy BH, Davenport P, Baylor J, *et al*. Inspiratory muscle strength training with behavioral therapy in a case of a rower with presumed exercise-induced paradoxical vocal-fold dysfunction. *Int J Pediatr Otorhinolaryngol* 2004;68:1327–32.
14. Mathers-Schmidt BA, Brilla LR. Inspiratory muscle training in exercise-induced paradoxical vocal fold motion. *J Voice* 2005;19:635–44.
15. Dickinson J, Whyte G, McConnell A. Inspiratory muscle training: a simple cost-effective treatment for inspiratory stridor. *Br J Sports Med* 2007;41:694–5.
16. Heimdal JH, Roksund OD, Halvorsen T, *et al*. Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise. *Laryngoscope* 2006;116:52–7.
17. Maat RC, Røksund OD, Halvorsen T, *et al*. Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations. *Eur Arch Otorhinolaryngol* 2009;266:1929–36.
18. Carlsen KH, Engh G, Mørk M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med* 2000;94:750–5.
19. Quanjer PH, Tammeling GJ, Cotes JE, *et al*. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5–40.
20. Knudson RJ, Lebowitz MD, Holberg CJ, *et al*. Changes in the normal maximal expiratory flow–volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725–34.
21. Boris M, Goldblatt A, Krigsman A. Laryngeal dysfunction: a common cause of respiratory distress, often misdiagnosed as asthma and responsive to antireflux therapy. *Allergy Asthma Proc* 2002;23:133–9.
22. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. *Am J Cardiol* 1978;41:69–75.
23. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;166:518–624.
24. Student. The probable error of a mean. *Biometrika* 1908;6:1–25.
25. Lydersen S. Statistical review: frequently given comments. *Ann Rheum Dis* 2015;74:323–5.
26. West BT WK, Galecki AT, Model LM. *A practical guide using statistical software*. London: Taylor & Francis Group, 2007.
27. Hilland M, Røksund OD, Sandvik L, *et al*. Congenital laryngomalacia is related to exercise-induced laryngeal obstruction in adolescence. *Arch Dis Child* 2016;101:443–8.
28. Maat RC, Hilland M, Røksund OD, *et al*. Exercise-induced laryngeal obstruction: natural history and effect of surgical treatment. *Eur Arch Otorhinolaryngol* 2011;268:1485–92.
29. Maat RC, Roksund OD, Olofsson J, *et al*. Surgical treatment of exercise-induced laryngeal dysfunction. *Eur Arch Otorhinolaryngol* 2007;264:401–7.
30. Sandnes A, Andersen T, Hilland M, *et al*. Laryngeal movements during inspiratory muscle training in healthy subjects. *J Voice* 2013;27:448–53.
31. Norlander K, Johansson H, Jansson C, *et al*. Surgical treatment is effective in severe cases of exercise-induced laryngeal obstruction: a follow-up study. *Acta Otolaryngol* 2015;135:1152–9.
32. Christensen P, Thomsen SF, Rasmussen N, *et al*. [Exercise-induced inspiratory stridor. An important differential diagnosis of exercise-induced asthma]. *Ugeskr Laeger* 2007;169:4047–50.
33. Walsted ES, Swanton LL, van van Someren K, *et al*. Laryngoscopy during swimming: a novel diagnostic technique to characterize swimming-induced laryngeal obstruction. *Laryngoscope* 2017;127:2298–301.
34. Olin JT, Clary MS, Fan EM, *et al*. Continuous laryngoscopy quantitates laryngeal behaviour in exercise and recovery. *Eur Respir J* 2016;48:1192–200.
35. Hargrove AE, Hargrove MB, Olin JT. Therapeutic laryngoscopy during exercise for treatment of refractory exercise-induced laryngeal obstruction. A personal experience. *Ann Am Thorac Soc* 2017;14:444–7.
36. Norlander K, Christensen PM, Maat RC, *et al*. Comparison between two assessment methods for exercise-induced laryngeal obstructions. *Eur Arch Otorhinolaryngol* 2016;273:425–30.
37. Walsted ES, Hull JH, Hvedstrup J, *et al*. Validity and reliability of grade scoring in the diagnosis of exercise-induced laryngeal obstruction. *ERJ Open Res* 2017;3:00070-2017.
38. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol* 2005;94:366–71.
39. Weinberger MM. Etiology of exercise-induced dyspnea: not just exercise-induced asthma or vocal cord dysfunction. *J Allergy Clin Immunol* 2008;121:269.
40. Christopher KL, Morris MJ. Vocal cord dysfunction, paradoxic vocal fold motion, or laryngomalacia? Our understanding requires an interdisciplinary approach. *Otolaryngol Clin North Am* 2010;43:43–66.
41. Brancatisano T, Collett PW, Engel LA. Respiratory movements of the vocal cords. *J Appl Physiol Respir Environ Exerc Physiol* 1983;54:1269–76.
42. Bartlett D. Respiratory functions of the larynx. *Physiol Rev* 1989;69:33–57.
43. Petcu LG, Sasaki CT. Laryngeal anatomy and physiology. *Clin Chest Med* 1991;12:415–23.
44. How SC, McConnell AK, Taylor BJ, *et al*. Acute and chronic responses of the upper airway to inspiratory loading in healthy awake humans: an MRI study. *Respir Physiol Neurobiol* 2007;157(2-3):270–80.
45. Baker SE, Sapienza CM, Martin D, *et al*. Inspiratory pressure threshold training for upper airway limitation: a case of bilateral abductor vocal fold paralysis. *J Voice* 2003;17:384–94.
46. Illi SK, Held U, Frank I, *et al*. Effect of respiratory muscle training on exercise performance in healthy individuals: a systematic review and meta-analysis. *Sports Med* 2012;42:707-24.
47. Morris MJ, Deal LE, Bean DR, *et al*. Vocal cord dysfunction in patients with exertional dyspnea. *Chest* 1999;116:1676–82.
48. Hjermstad MJ, Fayers PM, Haugen DF, *et al*. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage* 2011;41:1073–93.

Paper III (Study #III)

frontiers in Surgery

ORIGINAL RESEARCH
published: 31 July 2019
doi: 10.3389/fsurg.2019.00044

Severe Exercise-Induced Laryngeal Obstruction Treated With Supraglottoplasty

Astrid Sandnes[1,2], Magnus Hilland[3], Maria Vollsæter[2,4,5], Tiina Andersen[5,6], Ingvild Øvstebø Engesæter[3], Lorentz Sandvik[3], John-Helge Heimdal[3,7,8], Thomas Halvorsen[2,4], Geir Egil Eide[9,10], Ola Drange Røksund[2,4,11] and Hege H. Clemm[2,4]*

[1] Department of Internal Medicine, Innlandet Hospital Trust, Gjøvik, Norway, [2] Department of Clinical Science, University of Bergen, Bergen, Norway, [3] Department of Otolaryngology/Head and Neck Surgery, Haukeland University Hospital, Bergen, Norway, [4] Department of Pediatrics, Haukeland University Hospital, Bergen, Norway, [5] Norwegian Advisory Unit on Home Mechanical Ventilation, Thoracic Department, Haukeland University Hospital, Bergen, Norway, [6] Department of Physiotherapy, Haukeland University Hospital, Bergen, Norway, [7] Department of Surgery, Haukeland University Hospital, Bergen, Norway, [8] Department of Clinical Medicine, University of Bergen, Bergen, Norway, [9] Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway, [10] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, [11] The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway

OPEN ACCESS

Edited by:
Ramon Arturo Franco,
Massachusetts Eye & Ear Infirmary,
Harvard Medical School,
United States

Reviewed by:
Georgios Psychogios,
University Hospital of Ioannina, Greece
A. B. Zulkiflee,
University Malaya Medical Centre,
Malaysia

***Correspondence:**
Astrid Sandnes
astrid.sandnes@sykehuset-innlandet.no

Specialty section:
This article was submitted to
Otorhinolaryngology - Head and Neck
Surgery,
a section of the journal
Frontiers in Surgery

Received: 20 May 2019
Accepted: 16 July 2019
Published: 31 July 2019

Citation:
Sandnes A, Hilland M, Vollsæter M,
Andersen T, Engesæter IØ, Sandvik L,
Heimdal J-H, Halvorsen T, Eide GE,
Røksund OD and Clemm HH (2019)
Severe Exercise-Induced Laryngeal
Obstruction Treated With
Supraglottoplasty. Front. Surg. 6:44.
doi: 10.3389/fsurg.2019.00044

Introduction: Exercise induced laryngeal obstruction (EILO) is relatively common in adolescents, with symptoms often confused with exercise induced asthma. EILO often starts with medial or inward rotation of supraglottic structures of the larynx, whereas glottic adduction appears as a secondary phenomenon in a majority. Therefore, surgical treatment (supraglottoplasty) is used in thoroughly selected and highly motivated patients with pronounced symptoms and severe supraglottic collapse.

Aim: To investigate efficacy and safety of laser supraglottoplasty as treatment for severe supraglottic EILO by retrospective chart reviews.

Methods: The EILO register at Haukeland University Hospital, Bergen, Norway was used to identify patients who had undergone laser supraglottoplasty for severe supraglottic EILO, verified by continuous laryngoscopy exercise (CLE) test, during 2013–2015. Laser incision in both aryepiglottic folds anterior to the cuneiform tubercles and removal of the mucosa around the top was performed in general anesthesia. Outcomes were questionnaire based self-reported symptoms, and laryngeal obstruction scored according to a defined scheme during a CLE-test performed before and after surgery.

Results: Forty-five of 65 eligible patients, mean age 15.9 years, were included. Post-operatively, 38/45 (84%) patients reported less symptoms, whereas CLE-test scores had improved in all, of whom 16/45 (36%) had no signs of obstruction. Most improvements were at the supraglottic level, but 21/45 (47%) also improved at the glottic level. Two of 65 patients had complications; self-limiting vocal fold paresis and scarring/shortening of plica ary-epiglottica.

Conclusion: Supraglottoplasty improves symptoms and decreases laryngeal obstruction in patients with severe supraglottic EILO, and appears safe in highly selected cases.

Keywords: EILO, VCD, supraglottoplasty, larynx, exercise induced laryngeal obstruction

INTRODUCTION

Exercise induced laryngeal obstruction (EILO) is relatively common in young individuals (1–5). Symptoms are primarily prolonged and/or noisy inspiration and shortness of breath during ongoing high intensity exercise (6). Continuous laryngoscopy exercise test (CLE-test) (7) visualize the progression of obstruction during ongoing exercise from start to exhaustion, being essential for proper diagnosis and for subsequent planning and choice of treatment (8–11). Typically, the larynx appears endoscopically normal at rest whereas a transient, reversible narrowing occurs as exercise intensity increases. EILO is increasingly recognized as an important differential diagnosis to exercise-induced asthma/bronchoconstriction (EIB) in otherwise healthy adolescents (6, 10, 12–15).

Multiple treatment options are being applied for EILO, including surgical and non-surgical approaches, but so far none are based on high-quality evidence (2, 4, 10, 16). The etiology of EILO is likely to be heterogeneous, and at least two distinct phenotypes have been suggested; one characterized predominantly by a supraglottic medialization and/or collapse that clearly precedes the glottic obstruction, and another phenotype in which the glottic obstruction seems to incite the sequence of events (5, 6, 17). Treatment must be individualized and take into account these diverse findings (10). In a clinical setting, the role of surgery should be secondary to conservative treatment, such as properly guided breathing advice, speech therapy or inspiratory muscle training (4, 18–25). The literature suggests that surgery is beneficial in patients with a clearly predominant supraglottic involvement for whom EILO represent a significant clinical problem (4, 10, 11, 26). Follow-up studies for up to 5 years suggest lasting positive results (27, 28).

Surgery in patients with EILO is being performed at several centers, but a literature review revealed that results from only 72 cases have been published (26, 29). In this retrospective study, we investigated the efficacy and safety of laser supraglottoplasty for supraglottic EILO performed at our hospital, with CLE tests performed before and after surgery in all.

MATERIALS AND METHODS

Participants and Study Design

This study was based on a retrospective review of the *EILO-register* at Haukeland University Hospital, Norway. Our unit receives patients with suspected EILO from all Norway, and annually performs ~250 CLE tests. Patients who had been treated surgically with supraglottoplasty for EILO on clinical indications during 2013–2015 were included. First-line therapy for EILO at our institution (received by all patients) was physician-guided structured breathing advice while patients were observing their laryngeal responses on the monitor (biofeedback). Second-line treatment options were speech therapy or physician-guided inspiratory muscle training (IMT), with supraglottoplasty reserved for highly selected supraglottic cases. Indication for supraglottoplasty was based on symptom severity, the extent of the supraglottic collapse during a CLE-test (7), and patient motivation. Patients with laryngomalacia characteristics at rest [omega-shaped/juvenile epiglottis and prominent cuneiform tubercula's and/or redundant mucosa at the arytenoid region (30)], were excluded. Co-existing asthma had been treated according to guidelines (31), and asthma had been excluded as the cause of the patients' symptoms by a clinical interview and if in doubt, by performing spirometry after an exercise test (32). All patients had been informed about the surgical procedure and of risk factors.

The study was approved by the Committee on Medical Research Ethics of Western Norway (REK number 2016/1898), and informed written consent was obtained from the participants and/or their guardian.

Subjective Symptom Scores

Symptom scores before and after surgery were obtained using a questionnaire that also included demographic background variables. All patients answered these four questions (Q): Q1. *"Have your symptoms improved after the previous test?"*, *"yes"/"no"*; Q2. *"Rate your breathing problem on a scale from 0 to 10"*; Q3. *"I experience inspiratory breathing difficulty when I exercise,"* using a numeric rating scale (NRS) from 1 to 5 (1 = never, 2 = sometimes, 3 = often, 4 = almost every time, 5 = always); Q4. *"When you are physically active, how much are you bothered by your breathing difficulties?"*, using NRS from 1 to 5 (1 = nothing, 2 = a bit, 3 = pretty much, 4 = a lot, and 5 = disabling).

Spirometry and CLE-Test

Spirometry was performed with a Vmax 22© spirometer (*SensorMedics, Yorba Linda, CA, USA*) according to guidelines (33). A trans-nasal flexible fiberoptic laryngoscope (Olympus ENF-P3©, Tokyo, Japan), diameter 3.5 mm, introduced after applying a decongestive nasal spray (Rhinox©) and local anesthesia (Xylocaine©), was secured using a custom designed helmet in a position allowing for a good view of supraglottic structures and the vocal folds. Maximum voluntary ventilation (MVV) and ergospirometry data were collected in conjunction with the CLE-test using a Jaeger Oxycon Pro Cardiopulmonary Exercise testing system *(Viasys Health Care, Yorba Linda, CA, USA).* Continuous video-recorded laryngoscopy throughout a maximal cardiopulmonary exercise test on a treadmill *(Woodway ELG 70, Weil am Rhein, Germany)* was performed as previously described (the CLE-test) (7) before and after surgery. Simultaneous a computerized and modified Bruce ramp protocol coupled with integrated video-recording of the upper part of the body and sound-recordings was performed. The treadmill protocol increased speed and/or elevation every 1 min, aiming to reach maximum exercise capacity after 6–14 min (34). The test was considered successful if the patient continued until

Abbreviations: CLE-test, continuous laryngoscopy exercise test; EIB, exercise-induced asthma/bronchoconstriction; EIIS, exercise induced inspiratory symptoms; EILO, exercise induced laryngeal obstruction; FEV_1, forced expiratory volume in first second; IMT, inspiratory muscle training; NRS, numeric rating scale; PCA-muscle, posterior cricoarytenoideus muscle; Pi_{max}, maximal inspiratory mouth pressure; VAS, visual analog scale; VCD, vocal cord dysfunction.

exhaustion or was stopped by respiratory distress, preferably supported by a plateau in oxygen consumption and/or heart rate response.

Evaluation of CLE-Test

Laryngeal movements were scored as previously described at moderate and maximum exercise intensity, both at the glottic and supraglottic level (**Figure 1**) (2, 35). The assessments were done retrospectively, using the stored video-recorded CLE-tests presented in pairs (pre-post) to four experienced raters (HHC, ODR, MH and JHH). A blinded procedure was tested but proved impossible, as the surgical changes were impossible to hide. Thus, assessments were open and consensus-based. A score of $\geq$2 at either glottic or supraglottic level was interpreted as abnormal. Supraglottic EILO was defined by the supraglottic obstruction preceding the glottic obstruction and supraglottic (D) scores > glottic (C) scores at maximum exercise. Patients referred for supraglottoplasty had a supraglottic score $\geq$2, except one patient included because of large involvement from a retroflex epiglottis. Obstruction of the vocal folds (i.e., the glottic level) was not an exclusion criterion, but the supraglottic adduction should be the inciting event and clearly the predominant element of the obstruction.

Supraglottoplasty

All patients underwent surgery in general anesthesia with suspension micro-laryngoscopy and endoscopic supraglottoplasty with carbon dioxide laser, performed by one of two surgeons, experienced with laryngoplasty. The oral laser endotracheal (LET) tube was positioned posteriorly, protecting the interarytenoid area. A Lindholm/Benjamin laryngoscope was introduced into the vallecular exposing both aryepiglottic folds and epiglottis. The arytenoid was grasped with micro laryngeal forceps and pulled slightly forward and medially stretching the aryepiglottic fold, revealing the amount of abundant arytenoid tissue. Laser beams of 2–4 Watt focused with micro spot was utilized. The aryepiglottic fold was split anteriorly down to the level of the musculus aryepiglotticus approaching the cranial margin of plica ventricularis. Then tissue around the top of the cuneiform cartilages was removed in a circular pattern, creating a triangular shaped excision (**Figure 2**). In cases where the cuneiform tubercles were pointy and exposed in the excision, parts of this cartilage were included. The same procedure was performed bilaterally making sure to avoid endothelial damage to the interarytenoid covered by the LET-tube. In some cases with epiglottic involvement, epiglottotomy and rotation of the epiglottis toward the tongue base (epiglottopexy) were performed. Specific anatomic decisions tailored to the individual patient's anatomy were guided by findings on preoperative video-recording during CLE-test (26, 27, 36).

Statistical Methods

This was a cross-sectional pre-post study, with main outcomes being CLE-scores and symptom scores obtained before vs. after surgery, compared with Student's paired *t*-test. The CLE-scores are by nature ordinal and categorical, ranging from 0 to 3. Due to the few number of categories, data were calculated and reported as mean values with 95% confidence intervals (CI), as this is considered to provide more information than medians and interquartile ranges (37). To account for multiple correlated measurements in the same test subjects, mixed linear regression with fixed effects including three-way and two-way interactions was applied to address CLE-score changes before vs. after surgery obtained at moderate vs. maximal exercise intensity and at glottic vs. supraglottic laryngeal levels (38). All analyses were performed with SPSS version 24 (SPSS, Chicago, IL, USA).

RESULTS

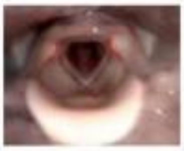
Sixty-five patients were eligible during the inclusion period. Twelve patients were excluded due to incomplete datasets, either pre- CLE-test or post-CLE-test, four patients did not consent to participation in the study and four patients were excluded retrospectively due to laryngeal findings characteristic of laryngomalacia. Thus, 45 patients were included; age 10–25 (mean 15.9) years, 14 males and 31 females. Baseline characteristics are outlined in **Table 1**. The post CLE-test was performed between 4 and 28 months (mean 13.4 months) after surgery. Lung function, distance completed on treadmill, minute ventilation (VE), peak VO_2 (ml/min) and maximal heart rate did not differ before vs. after surgery. MVV had increased significantly after surgery, and respiratory rate at peak exercise was reduced (**Table 2**). Epiglottotomy and/or epiglottopexy were performed as additional surgery in five of the 45 patients. As the CLE scoring system does not encompass ways to assess this type of surgery, these outcomes were not tabulated.

Subjective Symptom Scores

One patient did not complete the post-test questionnaire, for unknown reason. After surgery, perceived subjective symptoms improved in 38/44 (86%), were unchanged in 5/44 (11%), whereas 1/44 (2%) were unsure. The responses to the questions Q2, Q3 and Q4 improved significantly, and 25/43 (58%) patients (one did not answer this question) responded *nothing* or *a bit* to question Q4 (*When you are physically active, how much are you bothered by your breathing difficulties after surgery?)* (**Table 3**). Two patients reported more symptoms after surgery; one of whom had a post-operative complication.

Laryngeal Findings During Exercise (CLE-Score) and Complications

Laryngoscopy at rest was normal in all subjects. All patients had significantly lower CLE-scores after surgery, with sum-score (E) significantly reduced from 5.38 to 2.36; most improvements explained by reduced supraglottic scores at maximum exercise (CLE D-score) (**Table 4** and **Figure 3**). After surgery, 16/45 (36%) patients had no signs of laryngeal obstruction at maximum exercise intensity, i.e., CLE sum-score 0 or 1 (**Figure 4**). In 38/45 (84%) patients, CLE sum-score was reduced by 2 or more, reductions mainly occurring at the supraglottic level, as expected. However, in 21/45 also the glottic obstruction decreased at maximum intensity exercise, 10 of whom with a reduction of the glottic score of $\geq$2. In one patient, only the glottic obstruction improved, reducing CLE C-score (glottic

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

FIGURE 1 | Grading system of laryngeal obstruction according to Maat et al. (35), reproduced with permission.

FIGURE 2 | Supraglottoplasty with carbon dioxide laser on a patient with exercise induced laryngeal obstruction (EILO). Laser beams of 2–4 Watt focused with micro spot was utilized. The aryepiglottic fold was split anteriorly down to the level of the musculus aryepiglotticus approaching the cranial margin of plica ventricularis. Then tissue around the top of the cuneiform cartilages was removed in a circular pattern, creating a triangular shaped excision.

TABLE 1 | Baseline characteristics of the 45 patients included from the EILO register at Haukeland University Hospital, Bergen (Norway) who were surgically treated for EILO during 2013–2015.

Variable category	Pre-operative	Post-operative	P-value[a]
Female, n (% of group)	31/45 (68.9)		
Age in years, mean (range)	15.9 (10–25)	16.6 (11–27)	
Height in cm, mean (SD)	166.2 (10.3)	168.89 (9.4)	<0.001
Weight in kg, mean (SD)	57.7 (11.1)	62.21 (12.2)	<0.001
LUNGFUNCTION			
FVC, % of predicted (SD)	104.8 (14.1)	104.3 (14.7)	0.667
FEV_1, % of predicted (SD)	106.2 (13.1)	104.7 (13.5)	0.285
FEV_1/FIV_1 or FEF50/FIF50 > 1.5	2 (4.4)	2 (4.4)	
TREATMENT BEFORE SURGERY, n (%)			
First line conservative therapy only	30 (66.7)		
Second line therapy			
IMT	14 (31.1)		
Speech therapy	1 (2.2)		
LEVEL OF LARYNGEAL OBSTRUCTION, n (%)			
Only supraglottic	4 (9.1)		
Supraglottic ≥2 and glottic =1	22 (50.0)*		
Supraglottic ≥2 and glottic ≥2	18 (40.9)		

Values are ratios (% of group) or means (SD).
[a]*From Student's paired t-test.*
EILO, exercise induced laryngeal obstruction; IMT, inspiratory muscle training; FVC, forced vital capacity; FEV_1, forced expiratory volume in first second time; FEF50, forced expiratory flow at 50%; FIF50, forced inspiratory flow at 50%; SD, standard deviation.
One patient with supraglottic score 1 and glottic score 1 was included because of large involvement from a retroflex epiglottis (not assessed in the scoring system).

TABLE 2 | Ergospirometry data of the 45 patients included from the EILO register at Haukeland University Hospital, Bergen (Norway) who were surgically treated for EILO during 2013–2015.

Measures[a]	Pre-operative	Post-operative	p-value[b]
Distance on treadmill; m	677 (607, 748)	680 (623, 738)	0.858
Heart rate; per min	184 (180, 189)	177 (165, 189)	0.200
VO_2 max; ml/min	2760 (2,540, 2,979)	2822 (2,593, 3,051)	0.240
VO_2 max; ml/kg/min	47.9 (45, 51)	45.4 (43, 48)	0.003*
Breathing frequency; per min	49 (45, 53)	44 (42, 47)	0.005*
Minute ventilation; liters	92.0 (84, 100)	94.7 (86, 103)	0.340
MVV; liters/min	109 (99, 108)	120 (111, 129)	<0.001*
RER	1.16 (1.13, 1.19)	1.19 (1.15, 1.22)	0.079
Height; cm	166 (163, 169)	169 (166, 172)	<0.001*
Weight; kg	57.7 (54, 61)	62.2 (59, 66)	<0.001*

EILO, exercise induced laryngeal obstruction; VO_2 max, maximal oxygen consumption; MVV, maximal minute ventilation; RER, respiratory exchange ratio; CI, confidence interval.
[a]*All values are given as means (95% CI) at peak exercise.*
[b]*Paired sample t-test compare findings pre-operative vs. post-operative, *$p \leq 0.05$.*

TABLE 3 | Symptom scores based on four questions from the 45 patients included from the EILO register at the Haukeland University Hospital, Bergen (Norway) who were surgically treated for EILO during 2013–2015.

Question[a]	Pre-operative	Post-operative	p-value[b]
Q1. "Has your symptoms improved after the previous test?": n (%)		Yes 38 (86.4)[†]	
		No 5 (11.1)[†]	
		Unsure 1 (2.3)[†]	
Q2. Rate your breathing problems (NRS-scale from 0 to 10): mean (95% CI)	7.4 (6.6, 8.1)	2.8 (1.9, 3.6)	<0.001*
Q3[a]. "I experience inspiratory breathing difficulty when I exercise?" (NRS 0–5): mean (95% CI)	4.2 (3.9, 4.6)	2.6 (2.1, 3.0)	<0.001*
Q4[a]. "How much are you bothered by your breathing difficulties" (NRS 0–5): mean (95% CI)	3.8 (3.5, 4.2)	1.7 (1.4, 2.1)	<0.001*

EILO, exercise induced laryngeal obstruction; NRS, numeric rating scale (0–10); CI, confidence interval.
[†]*One patient did not answer the question.*
[a]*Answer options: 1 = never, 2 = sometimes, 3 = Often, 4 = Almost every time, 5 = Always.*
[b]*p-Value from student paired t-test.*
*$p \leq 0.05$.

score at maximum exercise) from 3 to 1. In two patients, the glottic obstruction worsened after surgery, but due to reduced supraglottic obstruction, the overall sum-score was reduced. One of these two had pre-operative glottic obstruction already at moderate intensity exercise, while the other was one of the two who experienced a post-operative complication.

In the mixed linear regression model the three-way interaction was not significant ($p = 0.231$), neither was the two-way interaction between exercise intensity (moderate vs. maximum) and level of obstruction (glottic vs. supraglottic) ($p = 0.232$). The final model included interactions between pre- vs. post-operative and moderate vs. maximum exercise intensity, and pre- vs. post-operative and glottic vs. supraglottic obstruction (both

TABLE 4 | Continuous laryngoscopy exercise (CLE) scores from the 45 patients included from the EILO register at Haukeland University Hospital, Bergen (Norway) who were surgically treated for EILO during 2013–2015[a].

CLE conditions	Pre-operative	Post-operative	Pre-post change	
	Mean (SD)	Mean (SD)	Mean (SD)	95% CI
MODERATE INTENSITY				
Glottic (CLE A)	0.27 (0.49)	0.09 (0.36)	0.18 (0.44)	(−0.08, 0.43)
Supraglottic (CLE B)	1.18 (0.96)	0.49 (0.73)	0.69 (0.73)	(0.43, 0.94)
MAXIMUM INTENSITY				
Glottic (CLE C)	1.51 (0.92)	0.84 (0.93)	0.67 (0.93)	(0.41, 0.92)
Supraglottic (CLE D)	2.42 (0.54)	0.93 (0.78)	1.49 (0.81)	(1.23, 1.74)
Sum score (CLE E)	5.38 (2.07)	2.36 (1.85)	3.02 (1.60)	(2.54, 3.50)[b]

CLE A, glottic obstruction at moderate intensity; CLE B, supraglottic obstruction at moderate intensity; CLE C, glottic obstruction at maximum intensity; CLE D, supraglottic obstruction at maximum intensity; CLE E, sum-score (A + B + C + D), see ***Figure 1*** *for illustrations on CLE score; CI, confidence interval; SD, standard deviation.*

[a]*In the final mixed linear regression model: CLE-score = constant + surgery + Intensity + location + surgery*Intensity + surgery*location, where all included effects were significant (p < 0.001).*

[b]*Estimates from Student's paired t-test, p < 0.001.*

p-values < 0.001). Thus, the CLE-score change after surgery was larger at maximum than at moderate exercise intensity, both glottic and supraglottic. Moreover, the CLE-score change after surgery was larger at the supraglottic than at the glottic level, regardless of exercise intensity.

Post-operative complications occurred in one of the included patients; a left vocal fold paresis that spontaneously resolved 3 years later. One of the 16 patients excluded due to missing pre-operative data, experienced post-operative scarring. This patient did not report post-operative breathing difficulties during daily activities, but persistent respiratory symptoms during exercise. This patient was offered a re-operation but declined. Hence, correct complication rate in our data was 3% (2/65).

Conservative Treatment

Second-line conservative treatment had been attempted in only 15/45 patients since no gold standard for EILO-treatment exist. Surgery was offered as a second or third-line option due to persistent symptoms and supraglottic obstruction. Fourteen patients underwent 6 weeks of inspiratory muscle training, whereas one underwent speech therapy over several weeks. The conservative treatment improved symptom scores (Q2) by 1.42 ($p = 0.027$), but patients perceived improvements as insufficient and their CLE-scores did not alter.

DISCUSSION

In this retrospective review of patients treated with laser supraglottoplasty for EILO, 86% reported perceived subjective symptom improvement. The CLE-sum score decreased in all patients; as expected most evident at the supraglottic level, but notably, there were also significant improvements at the glottic level. Our supraglottic findings are comparable to findings in previous studies (9, 27, 28, 36), thus supporting that laser supraglottoplasty is an efficient treatment in severe supraglottic EILO. The favorable glottic response from surgery was a novel finding. The study underlines the heterogeneity of EILO, and the importance of thorough phenotyping before making a treatment plan. Complications were rare.

Strength and Weakness

Our institution has performed more than 3,000 CLE-tests over a period of 15 years, with surgery performed in 3%. We have previously reported on 23 cases treated surgically for supraglottic EILO, not included in this study (27). This present case series is the largest published to date. It was a major strength that post-operative CLE-tests were used to assess outcome in all participants, contrasting some previous studies (9, 26–28, 39). Evaluations based on subjective patient reports are vulnerable to bias in both directions. There may be a positive placebo effect induced by the surgical procedure *per se*. On the other hand, patients can be disappointed that surgery treats only their EILO and not their physical capacity, as evident in this present study with virtually no changes in maximum oxygen consumption. Validity and reliability of the CLE scoring system varies somewhat between studies (28, 35, 40, 41); however, it seems reasonable to conclude that experience is a factor that influences these issues. In our study, four highly skilled raters scored the videos based on a consensus system, much like how CLE-tests are scored in everyday work. It has been suggested that familiarity with the test situation should somehow by itself improve the CLE-score; however, one third of our patients had tried additional conservative treatment before surgery with no significant reduction in CLE-scores with repeated tests. Similar maximum heart rate, minute volume and running distance at the pre-operative and post-operative CLE-test verified that the intensity was similar and that the laryngeal findings therefore could be compared.

Patients with EILO usually show normal supraglottic anatomy and laryngeal motion at rest and may show supraglottic appearance similar to laryngomalacia during exercise. Hence, Bent et al. labeled their observations "exercise induced laryngomalacia" (42). In order to avoid a mix between the adult type of laryngomalacia and EILO we chose to exclude four patients that had characteristics of laryngomalacia at rest (30). All four reported improvements of symptoms, and their mean CLE-sum scores improved substantially by 3.0 (data not shown).

An obvious weakness of this study was its retrospective design, with patients allocated to surgery based on clinical decisions, with no randomization, no blinding, and inconsistent follow-up times.

Supraglottoplasty as Treatment for EILO

Smith et al. first described endoscopic laser supraglottoplasty for supraglottic EILO in 1995 (43). A systematic review based on 72 patients suggested that the procedure is safe and indicates a favorable clinical response (29). In some published studies, it is difficult to verify the specific technique used (29). Careful assessment of our post-operative CLE-test files suggests that in some cases, more of the redundant supraglottic tissue could have been removed. On the other hand, a careful approach is required when performing surgery in otherwise healthy adolescents, particularly as long-term effects from surgery are

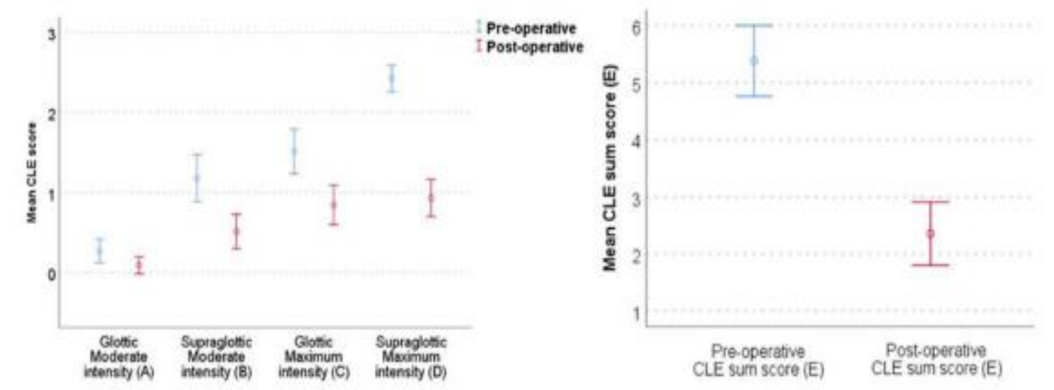


FIGURE 3 | Mean CLE sub scores and sum score (E) with 95% CIs at glottic (A + C) and supraglottic (B + D) level, and at moderate and at maximum intensity before and after supraglottoplasty from 45 patients included from the EILO register at Haukeland University Hospital, Bergen (Norway) who were treated with supraglottoplasty during 2013–2015. CLE, continuous laryngoscopy exercise test; EILO, exercise induced laryngeal obstruction; CI, confidence interval. See **Figure 1** for illustrations on CLE score (laryngeal obstruction scores).

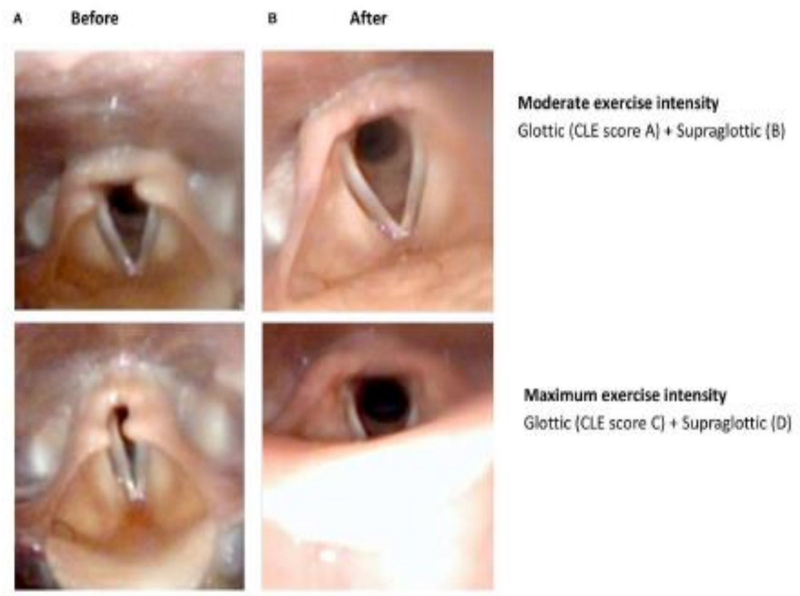


FIGURE 4 | Laryngoscopic findings in a patient with exercise-induced laryngeal obstruction (EILO), both supraglottic and glottic obstruction during maximum exercise intensity before **(A)** endoscopic supraglottoplasty and open laryngeal inlet after **(B)** endoscopic supraglottoplasty. Regarding CLE-scores, see **Figure 1** for illustrations.

unknown, and as normal laryngeal function during high-intensity exercise is poorly described (44). Also, the natural course of EILO is unknown. Laryngeal structures are described to become more rigid with age, and thus perhaps more stable (45–47). Patients in rapid growth should probably primarily be offered conservative treatment (10). A follow-up study up to 5 years showed persistent laryngeal obstruction during exercise in patients treated conservatively, despite decreasing self-reported symptoms (27). Symptomatic improvement could have been related to reduced physical activity with age, challenging the idea that EILO improves spontaneously with age (48, 49).

Post-operative Complications

Complications following supraglottoplasty for EILO have not been reported, possibly as few post-operative CLE-tests have been performed. Two studies have reported post-operative symptomatic complaints; one reporting dysphagia (9), and another breathing difficulties while exercising in cold air (27). In the present study, one participant experienced a self-limiting left vocal fold paresis, first believed to be due to luxation of the arytenoid cartilage inflicted by the intubation tube. However, extensive work-up revealed an Epstein-Barr viral infection and a large mediastinal thymus, possibly affecting the recurrent laryngeal nerve. Examination 3 years later showed normalized vocal fold movements and an open laryngeal inlet during exercise (CLE sum-score 0). Another patient excluded from participation as the pre-operative CLE-test could not be scored, had laryngeal scarring in the post-operative CLE-test. Previous laryngoscopies at rest revealed a laryngeal cyst, a condition that empirically is known to increase the risk for scarring. Patients with EILO are otherwise healthy young people, and therefore complication rates should be close to zero with potential gains carefully weighed against the risks (10, 26).

Glottic Adduction

It has been stated that glottic closure is likely to be unresponsive to surgical treatment (16). However, we found significant improvements also at the glottic laryngeal level. We cannot easily explain this, but perhaps the Bernoulli's principle is involved; i.e., removal of redundant supraglottic tissue leads to a wider supraglottic entrance, possibly reducing airflow turbulence and thus less negative luminal pressure, and therefore less adduction of the vocal folds below. The recently published method for measuring trans-laryngeal resistance appears as a promising possibility for an objective numeric outcome that might shed light on these issues (50).

CONCLUSION

Supraglottoplasty improves symptoms and reduces laryngeal obstruction in patients with a predominant supraglottic EILO, and appears safe and efficient in highly selected severe cases. Notably, supraglottoplasty might improve also glottic obstruction in patients with combined supraglottic and glottic obstruction. Our findings substantiate the heterogeneity of EILO, with phenotypes that require different treatment approaches. Risk of complications calls for careful selection of patients based on a multidisciplinary approach, with conservative treatment carefully tested prior to surgery. There is an urgent need for randomized studies and longer follow-up periods.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Committee on Medical Research Ethics of Western Norway (REK number 2016/1898). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AS and MH: substantial contributions to the conception of the work, data collection, and drafting the manuscript. MV: substantial contributions to the conception of the work, data collection, critically revising the work, and final approval of the version to be published. TA: substantial contributions to the conception of the work, critically revising the work, and final approval of the version to be published. IE and LS: substantial contributions to the conception of the work and data collection. J-HH substantial contributions to the conception of the work and critically revising the work and interpretation of data, final approval of the version to be published. TH: substantial contributions to the conception of the work and critically revising the work and interpretation of data, final approval of the version to be published. GE: substantial contributions to statistical analysis and interpretation of the work, final approval of the version to be published. OR and HC: substantial contributions to the conception of the work, data collection and critically revising the work and interpretation of data, final approval of the version to be published. All authors contributed to manuscript revision, read and approved the submitted version.

ACKNOWLEDGMENTS

Major funding institutions: Haukeland University Hospital and University of Bergen.

REFERENCES

1. Christensen PM, Thomsen SF, Rasmussen N, Backer V. Exercise-induced laryngeal obstructions: prevalence and symptoms in the general public. *Eur Arch Otorhinolaryngol.* (2011) 268:1313–9. doi: 10.1007/s00405-011-1612-0
2. Halvorsen TW, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. *Eur Respir J.* (2017) 50:1602221. doi: 10.1183/13993003.02221-2016
3. Johansson H, Norlander K, Berglund L, Janson C, Malinovschi A, Nordvall L, et al. Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. *Thorax.* (2015) 70:57–63. doi: 10.1136/thoraxjnl-2014-205738
4. Liyanagedera S, McLeod R, Elhassan HA. Exercise induced laryngeal obstruction: a review of diagnosis and management. *Eur Arch Otorhinolaryngol.* (2017) 274:1781–9. doi: 10.1007/s00405-016-4338-1
5. Nielsen EW, Hull JH, Backer V. High prevalence of exercise-induced laryngeal obstruction in athletes. *Med Sci Sports Exerc.* (2013) 45:2030–5. doi: 10.1249/MSS.0b013e318298b19a
6. Roksund OD, Maat RC, Heimdal JH, Olofsson J, Skadberg BT, Halvorsen T. Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. *Respir Med.* (2009) 103:1911–8. doi: 10.1016/j.rmed.2009.05.024
7. Heimdal JH, Roksund OD, Halvorsen T, Skadberg BT, Olofsson J. Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise. *Laryngoscope.* (2006) 116:52–7. doi: 10.1097/01.mlg.0000184528.16229.ba
8. Christensen PM, Heimdal JH, Christopher KL, Bucca C, Cantarella G, Friedrich G, et al. ERS/ELS/ACCP 2013 international consensus conference nomenclature on inducible laryngeal obstructions. *Eur Respir Rev.* (2015) 24:445–50. doi: 10.1183/16000617.00006513
9. Mehlum CS, Walsted ES, Godballe C, Backer V. Supraglottoplasty as treatment of exercise induced laryngeal obstruction (EILO). *Eur Arch Otorhinolaryngol.* (2016) 273:945–51. doi: 10.1007/s00405-015-3823-2

10. Roksund OD, Heimdal JH, Clemm H, Vollsaeter M, Halvorsen T. Exercise inducible laryngeal obstruction: diagnostics and management. *Paediatr Respir Rev.* (2017) 21:86–94. doi: 10.1016/j.prrv.2016.07.003
11. Roksund OD, Heimdal JH, Olofsson J, Maat RC, Halvorsen T. Larynx during exercise: the unexplored bottleneck of the airways. *Eur Arch Otorhinolaryngol.* (2015) 272:2101–9. doi: 10.1007/s00405-014-3159-3
12. Christopher KL, Morris MJ. Vocal cord dysfunction, paradoxic vocal fold motion, or laryngomalacia? Our understanding requires an interdisciplinary approach. *Otolaryngol Clin North Am.* (2010) 43:43–66, viii. doi: 10.1016/j.otc.2009.12.002
13. Griffin SA, Walsted ES, Hull JH. Breathless athlete: exercise-induced laryngeal obstruction. *Br J Sports Med.* (2018) 52:1211–2. doi: 10.1136/bjsports-2018-099159
14. Lakin RC, Metzger WJ, Haughey BH. Upper airway obstruction presenting as exercise-induced asthma. *Chest.* (1984) 86:499–501.
15. Rundell KW, Spiering BA. Inspiratory stridor in elite athletes. *Chest.* (2003) 123:468–74. doi: 10.1378/chest.123.2.468
16. Haines J, Hull JH, Fowler SJ. Clinical presentation, assessment, and management of inducible laryngeal obstruction. *Curr Opin Otolaryngol Head Neck Surg.* (2018) 26:174–9. doi: 10.1097/MOO.0000000000000452
17. Nordang L, Norlander K, Walsted ES. Exercise-induced laryngeal obstruction–an overview. *Immunol Allergy Clin North Am.* (2018) 38:271–80. doi: 10.1016/j.iac.2018.01.001
18. Clemm HSH, Sandnes A, Vollsaeter M, Hilland M, Heimdal JH, Roksund OD, et al. The heterogeneity of exercise-induced laryngeal obstruction. *Am J Respir Crit Care Med.* (2018) 197:1068–9. doi: 10.1164/rccm.201708-1646IM
19. Dickinson J, Whyte G, McConnell A. Inspiratory muscle training: a simple cost-effective treatment for inspiratory stridor. *Br J Sports Med.* (2007) 41(discussion 695):694–5. doi: 10.1136/bjsm.2006.033654
20. Mathers-Schmidt BA, Brilla LR. Inspiratory muscle training in exercise-induced paradoxical vocal fold motion. *J Voice.* (2005) 19:635–44. doi: 10.1016/j.jvoice.2005.03.005
21. Olin JT, Deardorff EH, Fan EM, Johnston KL, Keever VL, Moore CM, et al. Therapeutic laryngoscopy during exercise: a novel non-surgical therapy for refractory EILO. *Pediatr Pulmonol.* (2017) 52:813–9. doi: 10.1002/ppul.23634
22. Ruddy BH, Davenport P, Baylor J, Lehman J, Baker S, Sapienza C. Inspiratory muscle strength training with behavioral therapy in a case of a rower with presumed exercise-induced paradoxical vocal-fold dysfunction. *Int J Pediatr Otorhinolaryngol.* (2004) 68:1327–32. doi: 10.1016/j.ijporl.2004.04.002
23. Sandnes A, Andersen T, Clemm HH, Hilland M, Vollsaeter M, Heimdal JH, et al. Exercise-induced laryngeal obstruction in athletes treated with inspiratory muscle training. *BMJ Open Sport Exerc Med.* (2019) 5:e000436. doi: 10.1136/bmjsem-2018-000436
24. Shaffer M, Litts JK, Nauman E, Haines J. Speech-language pathology as a primary treatment for exercise-induced laryngeal obstruction. *Immunol Allergy Clin North Am.* (2018) 38:293–302. doi: 10.1016/j.iac.2018.01.003
25. Sullivan MD, Heywood BM, Beukelman DR. A treatment for vocal cord dysfunction in female athletes: an outcome study. *Laryngoscope.* (2001) 111:1751–5. doi: 10.1097/00005537-200110000-00016
26. Heimdal JH, Maat R, Nordang L. Surgical intervention for exercise-induced laryngeal obstruction. *Immunol Allergy Clin North Am.* (2018) 38:317–24. doi: 10.1016/j.iac.2018.01.005
27. Maat RC, Hilland M, Roksund OD, Halvorsen T, Olofsson J, Aarstad HJ, et al. Exercise-induced laryngeal obstruction: natural history and effect of surgical treatment. *Eur Arch Otorhinolaryngol.* (2011) 268:1485–92. doi: 10.1007/s00405-011-1656-1
28. Norlander K, Johansson H, Jansson C, Nordvall L, Nordang L. Surgical treatment is effective in severe cases of exercise-induced laryngeal obstruction: a follow-up study. *Acta Otolaryngol.* (2015) 135:1152–9. doi: 10.3109/00016489.2015.1062548
29. Siewers K, Backer V, Walsted ES. A systematic review of surgical treatment for supraglottic exercise-induced laryngeal obstruction. *Laryngosc Investig Otolaryngol.* (2019) 4:227–33. doi: 10.1002/lio2.257
30. Hilland M, Roksund OD, Sandvik L, Haaland O, Aarstad HJ, Halvorsen T, et al. Congenital laryngomalacia is related to exercise-induced laryngeal obstruction in adolescence. *Arch Dis Child.* (2016) 101:443–8. doi: 10.1136/archdischild-2015-308450
31. Guidelines G. *GINA Report, Global Strategy for Asthma Management and Prevention.* (2018) Available online at: https://ginaasthma.org.
32. Carlsen KH, Engh G, Mork M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med.* (2000) 94:750–5. doi: 10.1053/rmed.2000.0809
33. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J.* (1993) 6:5–40. doi: 10.1183/09041950.005s1693
34. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. *Am J Cardiol.* (1978) 41:69–75.
35. Maat RC, Roksund OD, Halvorsen T, Skadberg BT, Olofsson J, Ellingsen TA, et al. Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations. *Eur Arch Otorhinolaryngol.* (2009) 266:1929–36. doi: 10.1007/s00405-009-1030-8
36. Maat RC, Roksund OD, Olofsson J, Halvorsen T, Skadberg BT, Heimdal JH. Surgical treatment of exercise-induced laryngeal dysfunction. *Eur Arch Otorhinolaryngol.* (2007) 264:401–7. doi: 10.1007/s00405-006-0216-6
37. Lydersen S. Statistical review: frequently given comments. *Ann Rheum Dis.* (2015) 74:323–5. doi: 10.1136/annrheumdis-2014-206186
38. West BT, Welch KB, Galecki AT. *Linear Mixed Model. A Practical Guide Using Statistical Software.* London: Taylor & Francis Group (2007).
39. Richter GT, Rutter MJ, deAlarcon A, Orvidas LJ, Thompson DM. Late-onset laryngomalacia: a variant of disease. *Arch Otolaryngol Head Neck Surg.* (2008) 134:75–80. doi: 10.1001/archoto.2007.17
40. Norlander K, Christensen PM, Maat RC, Halvorsen T, Heimdal JH, Moren S, et al. Comparison between two assessment methods for exercise-induced laryngeal obstructions. *Eur Arch Otorhinolaryngol.* (2016) 273:425–30. doi: 10.1007/s00405-015-3758-7
41. Walsted ES, Hull JH, Hvedstrup J, Maat RC, Backer V. Validity and reliability of grade scoring in the diagnosis of exercise-induced laryngeal obstruction. *ERJ Open Res.* (2017) 3:e00070–2017. doi: 10.1183/23120541.00070-2017
42. Bent JPIII, Miller DA, Kim JW, Bauman NM, Wilson JS, Smith RJ. Pediatric exercise-induced laryngomalacia. *Ann Otol Rhinol Laryngol.* (1996) 105:169–75. doi: 10.1177/000348949610500301
43. Smith RJ, Bauman NM, Bent JP, Kramer M, Smits WL, Ahrens RC. Exercise-induced laryngomalacia. *Ann Otol Rhinol Laryngol.* (1995) 104:537–41. doi: 10.1177/000348949510400707
44. Beaty MM, Wilson JS, Smith RJ. Laryngeal motion during exercise. *Laryngoscope.* (1999) 109:136–9.
45. Fried MP. *The Larynx. 2nd Edn.* St. Louis, MO: Mosby (1996) 18–45.
46. Kahane JC. Growth of the human prepubertal and pubertal larynx. *J Speech Hear Res.* (1982) 25:446–55.
47. Wysocki J, Kielska E, Orszulak P, Reymond J. Measurements of pre- and postpubertal human larynx: a cadaver study. *Surg Radiol Anat.* (2008) 30:191–9. doi: 10.1007/s00276-008-0307-8
48. Doshi DR, Weinberger MM. Long-term outcome of vocal cord dysfunction. *Ann Allergy Asthma Immunol.* (2006) 96:794–9. doi: 10.1016/S1081-1206(10)61341-5
49. Zalzal GH, Anon JB, Cotton RT. Epiglottoplasty for the treatment of laryngomalacia. *Ann Otol Rhinol Laryngol.* (1987) 96:72–6. doi: 10.1177/000348948709600118
50. Fretheim-Kelly Z, Halvorsen T, Heimdal JH, Strand E, Vollsaeter Zoe M, Clemm H, et al. Feasibility and tolerability of measuring translaryngeal pressure during exercise. *Laryngoscope.* (2019). doi: 10.1002/lary.27846. [Epub ahead of print].

Conflict of Interest Statement: Haukeland University Hospital owns parts of US patent No. 11/134551, protecting the commercial rights of the CLE-test.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Graphic design: Communication Division, UIB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 9788230858356 (print)
9788230857731 (PDF)