HØGSKOLEN I BERGEN

Mastergradsstudium i klinisk fysioterapi

Mastergradsoppgave

Laryngeal movements in healthy subjects during mechanical insufflation-exsufflation

Laryngeale bevegelser hos friske ved bruk av hostemaskinen

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PREFACE AND ACKNOWLEDGEMENTS

According to our teacher Hildegunn Lygren, *"Research is like studying the brick wall of knowledge, to find a hole on it, and to fill it".* Several times I have scratched my head about the patients who do not success in treatment with mechanical cough device, probably due to laryngeal response. Besides, I am not alone; knowledge on this field is lacking. When I heard that Ola D. Røksund would be my supervisor, I got the courage to ask him if the method of transnasal laryngoscopy they use during a treadmill test to diagnose exercise induced laryngeal obstruction, was possible to use also during the use of this cough device. Just after a week, Ola and I tried this out with the help of an otolaryngologist Magnus Hilland, and it turned out that I had found my hole on this brick wall of knowledge.

Even if this has been an independent process, I am proud to present that the project is collaboration between Norwegian Centre of Excellence for Home Mechanical Ventilation at Thoracic Department, Departments of Neurology, Physiotherapy, Otolaryngology, Pediatrics and Medical Technical at the Haukeland University Hospital, Bergen, Norway and Bergen University College. I want to thank all these institutions for collaboration and I am looking forward to work with you further.

"If I have seen further it is by standing on the shoulders of giants".

Isaac Newton

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Bergen, June 2nd 2012

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ABSTRACT

Introduction: Airway clearance is one of the main elements in respiratory physiotherapy. Mechanical insufflation-exsufflation (MI-E) is a mechanical cough device that works through application of a positive pressure during inspiration and a negative pressure during expiration. It is the most effective approach to increase peak cough flow in patients with neuromuscular diseases, thereby potentially augmenting airway clearance. Co-ordinated movements of the glottis are probably crucial for effect, but laryngeal response patterns to MI-E have not been studied.

Aims: Visualize and describe laryngeal response patterns to MI-E in healthy subjects.

Design: A descriptive observational study with cross-sectional design.

Methods: Twenty healthy volunteers aged 21-29 (mean 24) years were examined with video recorded flexible transnasal fiberoptic laryngoscopy during MI-E (Cough Assist®, Respironics, USA) according to a standardized protocol applying pressures of ±20 to ±50 cmH_2O. Subjects were instructed to inhale during insufflation and both to actively exhale and cough during exsufflation. Thereafter, single insufflation was applied using the same positive pressures followed by voluntary cough, assisted with a manual thrust, but with no applied negative pressures. Laryngeal movements were assessed by video recordings.

Results: Abduction of the vocal folds was observed in all subjects both during the phases of insufflation and exsufflation. Nineteen of twenty subjects managed to coordinate the glottic closure when instructed to cough. When instructed to cough with no applied negative pressure, the same pattern was observed. When instructed simply to exhale during exsufflation, the glottis stayed open in the majority of the subjects. In addition to these most common movements, a variety of other movements were observed more infrequently, i.e. subsequent narrowing of vocal folds, adduction of aryepiglottic folds, retroflex movement of the epiglottis, hypopharyngeal constriction and backward movement of the base of the tongue.

Conclusion: The larynx can be studied with transnasal laryngoscopy during MI-E in healthy individuals. Although a variety of response patterns were observed, most healthy subjects managed to coordinate their glottic opening and closure according to task, irrespective of pressure settings on the MI-E. The study suggests that laryngoscopy may offer valuable information when MI-E is being used in patients with bulbar muscle weakness. This may contribute to better clinical respiratory physiotherapy treatment in these patients.

Keywords: Mechanical insufflation-exsufflation, mechanical assisted cough, larynx, fiberoptic laryngoscopy

SAMMENDRAG

Introduksjon: Sekretmobilisering er en viktig del av lungefysioterapi. Hostemaskinen fyller (insuflerer) lungene med positivt trykk og tømmer (eksuflerer) lungene med negativt trykk. Teknikken kalles for mekanisk insuflasjon-eksuflasjon og er det mest effektive tiltak for å øke luftstrømshastigheten ved hoste hos personer med neuromuskulære lidelser. En slik økt luftstrømshastighet tenkes å forbedre sekretmobilisering hos disse pasientene, men forutsetter koordinerte bevegelser på stemmebåndsnivå. Strupens bevegelser ved bruk av hostemaskinen har ikke blitt undersøkt tidligere.

Hensikt: Visualisere og beskrive strupens responsmønster ved bruk av hostemaskinen hos friske forsøkspersoner.

Design: Beskrivende observasjonell studie med tverrsnittsdesign.

Metode: Tjue friske frivillige på alder 21-29 (gj.snitt 24) år ble undersøkt med fleksibelt laryngoskopi gjennom nesen med video opptak, mens hostemaskinen (Cough Assist®, Respironics, USA) ble brukt med standardisert protokoll av trykkinnstillinger fra ±20 til ±50 cmH_2O. Det ble gitt instruksjon til å puste inn ved insuflasjon og både aktivt puste ut og hoste under eksuflasjon. Deretter ble en enkel insuflasjon gitt med de samme positive trykkene fra hostemaskinen, fulgt av voluntær hoste kombinert med manuell hostestøtte uten negativ trykk (eksuflasjon). Strupens bevegelser ble vurdert fra videoopptakene.

Resultater: Abduksjon av stemmebåndene ble observert hos alle både under insuflasjon og eksuflasjon. Nitten av tjue forsøkspersoner klarte å koordinere lukking av glottis når de ble instruert til å hoste. Samme mønster ble observert når forsøkspersonene ble instruert til å hoste uten eksuflasjon. Ved instruksjon av aktiv utpust var glottis åpen hos de fleste. I tillegg til de overfor nevnte prominente bevegelsene ble en stor variasjon av andre laryngeale bevegelser observert, dvs. påfølgende forsnevring av stemmebåndene, abduksjon og adduksjon av aryepiglottiske foldene, retrofleks bevegelse av epiglottis, hypopharyngeal obstruksjon og bakover bevegelse av tungebasen.

Konklusjon: Strupens bevegelser hos friske ved bruk av hostemaskinen kan undersøkes med laryngoskopi. Selv om stor variasjon i de laryngeale bevegelsene ble observert, de fleste friske forsøkspersoner klarte å koordinere lukking og åpning på stemmebåndsnivå i forhold til oppgavene selv om trykkforholdene ble endret. Laryngoskopi kan trolig bidra med verdifull informasjon når hostemaskinen blir brukt hos pasienter med bulbær dysfunksjon. Dette kan forbedre den kliniske lungefysioterapeutiske behandlingen av disse pasientene.

Nøkkelord: mekanisk insuflasjon-eksuflasjon, hostemaskin, strup, fiberoptisk laryngoskopi

LIST OF ABBREVIATIONS

ALS	Amyotrophic lateral sclerosis
BMI	Body Mass Index
CLE-test	Continious laryngoscopy exercise test
CPAP	Continuous Positive Airway Pressure
CT	Computer tomography
FET	Forced expiratory technique
FEV1	Forced expiratory volume in the first second
FVC	Forced vital capacity
G	Glottic
H	Hypopharyngeal
MI	Mechanical insufflation
MI-E	Mechanical insufflation-exsufflation
n	Sample size
NMD	Neuromuscular disease
PCF	Peak cough flow
PEF	Peak expiratory flow
p	p-value
Pi_{max}	Maximal inspiratory mouth pressure
Pe_{max}	Maximal expiratory mouth pressure
S	Subglottic
SD	Standard deviation
TFL	Transnasal fiberoptic laryngoscopy
VC	Vital capacity
VCD	Vocal cord dysfunction

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1. INTRODUCTION

An effective cough is dependent of inspiratory muscles to increase lung volume, expiratory muscles to produce high thoracoabdominal pressures and laryngeal muscles to coordinate both glottic opening and closure (Leith, 1985). All these phases can be impaired in persons with neuromuscular diseases (NMD) resulting in low peak cough airflow (PCF), which is inadequate to move mucus from the airways (Bach, 1993; Sancho et al., 2004b). Retained airway secretions lead to reduced gas exchange and will form favorable conditions for bacteria to grow. This may lead to pneumonia, which is the most frequent cause of death in this patient group. Therefore, it is important both to prevent and to treat effectively accumulation of airway secretions in persons with NMD. (Boitano, 2006).

The aim of the respiratory physiotherapy in persons with NMD is to increase inspiratory volumes and expiratory flow (Gosselink et al., 2008; Bott et al., 2009). Respiratory physiotherapy in NMD consists of daily deep breaths to prevent atelectasis and stiffness of thorax, in addition to airway clearance and especially effective assisted cough (Bott et al., 2009; Finder, 2010).

Mechanical insufflation-exsufflation (MI-E) is a therapeutic technique to assist cough and to apply a mechanical deep breath. It is currently the most effective technique for eliminating airway secretions in persons with muscle weakness due to a wide variety of NMD. (Homnick, 2007; Anderson, Hasney & Beaumont, 2005). The effectiveness of MI-E is thought to be based on enhancement of PCF to level that is necessary move the airway secretions in persons with NMD (Chatwin et al., 2003; Chatwin & Simonds, 2009; Fauroux et al., 2008; Hanayama, Ishikawa & Bach, 1997; Miske et al., 2004; Sancho et al., 2004b; Winck et al., 2004; Sivasothy et al., 2001; Bach, 1994 ; 1993; Mustfa et al., 2003; Pillastrini et al., 2006). In Norway, MI-E devices became available in 2001 and the Norwegian public health care system provides MI-E for eligible patients (Andersen, Tollefsen & Fondenes, 2011).

Personal experience from clinical work

My background is as a physiotherapist, employed by The Norwegian Centre of Excellence for Home Mechanical Ventilation. Home mechanical ventilation provides long term

mechanical ventilation support for persons with chronic respiratory failure, who predominantly have a neuromuscular disorder. Long term mechanical ventilation is provided mostly by mask (non-invasive) and more rarely by tracheostomy, i.e. via hole in the throat (invasive). (Aarrestad et al., 2012).

In my clinical work, focusing on airway clearance in patients with chronic respiratory failure, mechanical cough devices utilizing the technique of MI-E is used on a daily basis. The non-invasive use of MI-E requires ability of the patient to co-operate in addition to the required cognitive abilities. My clinical experience indicates substantial benefit of MI-E on airway clearance in most neuromuscular patients. This effect may be observed directly as an immediate clearance of airway secretions, but also by improved long-term outcome in the management of colds and prevention of chest infections. My impression is that requirements for hospitalizations and even tracheostomy may be reduced.

However, patients with bulbar dysfunction (an intrinsic laryngeal weakness), especially persons with Amyotrophic lateral sclerosis (ALS), remains challenging to treat successfully with non-invasive MI-E technique. Particularly in ALS patients the clinical response to non-invasive use of MI-E is variable, which indicates a certain motor dysfunction of the upper airways. Some ALS patients, including those with bulbar dysfunction, seem to be able to succeed in managing the technique, whereas some express a sensation of being "unable to breath in or out" with the MI-E device. In some cases the effect of MI-E seems to be reduced in parallel to disease progression and deteriorating bulbar dysfunction. It is difficult to predict beforehand which individuals will succeed or not as there are no evidence based predictive factors. In practice, a therapeutic trial is conducted in most neuromuscular patients who present with a manifest cough problem.

Evidence based knowledge of the issue

Research in the field of MI-E and intrinsic laryngeal weakness is lacking. Some studies confirm that MI-E can increase the ability to clear airway secretions in persons with ALS, but mostly in those without bulbar dysfunction (Sancho et al., 2004b; Perrin, 2006; Mustfa et al., 2003; Bach, 1995; Winck et al., 2004; Hanayama, Ishikawa & Bach, 1997). One study, by Sancho et al. (2004b), reported that patients with bulbar muscle weakness due to ALS not always were able to reach an adequate PCF when using MI-E. To increase the

understanding of this observation, the same researchers examined three study subjects at baseline conditions and during application of mechanical exsufflation with a Computer Tomography (CT) scanning of their upper airways (pharynx and oropharynx). Failure to increase PCF to a sufficient level in patients with bulbar dysfunction was explained by dynamic collapse of the upper airway during exsufflation. Although they did not examine directly the laryngeal level, they generated a hypothesis that coordinated movements of the glottis probably are crucial for effectiveness of MI-E applied via a mask. (Sancho et al., 2004b).

If glottic movements are crucial for success with MI-E, this is an important issue to investigate further. The knowledge of laryngeal response patterns to MI-E is central in order to improve the clinical physiotherapy treatment and to maintain quality of life in persons with ALS. To my knowledge, the laryngeal response patterns to MI-E have not previously been studied. To increase the understanding of this phenomenon, visualization of the laryngeal movement patterns during MI-E is desirable.

An integrated set-up with transnasal fiberoptic laryngoscopy (TFL) has been used during an ongoing maximum exercise test. The test has been named Continious laryngoscopy exercise test (CLE-test) and was developed at our hospital aimed to diagnose exercise induced upper airway flow limitation both in children and adults. TFL is a well-tolerated method and easy to perform. (Heimdal et al., 2006; Maat et al., 2009; Røksund et al., 2009). Theoretically, I can see no reasons why the method of TFL could not be used to visualize the larynx during MI-E and thereby be a helpful tool for describing the laryngeal movements during MI-E maneuvers in bulbar patients.

1.1. Aims of the study

The present study is performed in the context of a master degree, which limits the extent of time available. This master thesis represents a pre-study prior to a study of persons with ALS with the purpose to investigate the feasibility of transnasal fiberoptic laryngoscopy during MI-E and to investigate normal laryngeal response pattern(s) to the pressure variations applied during treatment with MI-E

The aim, therefore, is to visualize and describe the characteristics of laryngeal movements through fiberoptic laryngoscopy recordings during the whole cycle of MI-E, in healthy subjects. MI-E will be used with clinically used pressure settings and verbal instructions. The intention is to establish a foundation for further examination in patients.

1.2. Research questions

I. Is it possible to use the TFL-method to visualize and record laryngeal movements throughout the MI-E protocol?
II. Is it possible to use the TFL-method recordings to describe the characteristics of the laryngeal movements throughout the MI-E protocol?
III. Can this description be used as a foundation in examination of persons with neuromuscular diseases with the purpose to optimize the MI-E treatment?

1.3. Theoretical framework

In the present study I will try to shed a light on the issue of this "black box of the larynx" by visualizing, observing and describing laryngeal movements during MI-E. A look inside the body by using biomedical research can increase the knowledge of what factors of the larynx that prevents success with MI-E in some cases. The technique (MI-E) this study focus on, and the method (TFL) used, are both of mechanical art. Still, the present study is conducted in synergy according to framework of motor control (Shumway-Cook & Woollacott, 2007) and health promotion (Domholdt, 2005: p.48-50).

The field of physiotherapy involves the analysis of body, movement and function. The nature of movements and how movements are controlled constitute the theory of motor control. This can be defined as the ability to regulate or direct the mechanisms which are essential for the movements. These mechanisms include both the central nervous system, sensory information from the environment and the body, our self-perception, the task we perform and the environment we are in. There is an understanding that the nature of movement is not alone organized by motor output from nervous system to muscles, but both the task and the environmental demands influence how movement is organized. Movements are often studied and described in relation to specific actions with the

understanding that control processes will provide insight into principles for how the movements are controlled. (Shumway-Cook & Woollacott, 2007: p.4-5).

Clinical interventions aiming to improve the motor control in patients with neurological dysfunction are based on understanding of the nature and cause of normal movement, as well as an understanding of the basis for abnormal movement. (Shumway-Cook & Woollacott, 2007: p.8). The subjects in this pilot study are healthy volunteers with no indications to use MI-E. However, knowledge of what is normal is necessary to be able to define pathological limitations in real patients. In this study MI-E will be used as similarly as possible to its clinical use in respiratory physiotherapy; as regards pressure settings and instructions given. Results from research examining healthy humans, who are using a technique designed for patients, are not directly applicable to a clinical setting. Practically, such research may lead to modification of theory and may in turn lead clinicians to rethink the ways we are treating our patients. (Domholdt, 2005: p.18 & 48).

In clinical practice, MI-E technique is widely used by respiratory physiotherapists and this will influence the jargon of this written dissertation. The data generated in this study is of quantitative nature. In addition, snapshots of the laryngeal positions during the intervention will visualize the results.

2. BACKGROUND

2.1. Respiratory physiotherapy and airway clearance

Respiratory physiotherapy is an aspect of physiotherapy practice, and can be defined as physical management of problems, or potential problems, in persons with respiratory conditions to obtain and maintain function and to minimize progression of the disease (Cystic Fibrosis Worldwide, 2008). Respiratory physiotherapy consists of elements from physical exercise testing and prescription, rehabilitation, breathing techniques, positioning and airway clearance (Bott et al., 2009).

Airway clearance also referred to as a mucus clearance or secretion clearance is one of the main elements of respiratory physiotherapy. It is a critical aspect of respiratory care, since impairments in airway clearance are associated with complications, such as respiratory tract infections, which can lead to life-threatening complications for patients with different diseases (Finder, 2010). Airway clearance regimes should be efficient, easy to use and to teach. Moreover one should be able to it independently or with the help of an assistant, it should improve lung function and should not cause hypoxemia or be uncomfortable. Last but not least, it should be flexible and adaptable to the changing needs of the individual patient. (Pryor, 1999).

Physiotherapy for clearing airway secretions consists of techniques both to support mucociliary clearance and to augment coughing (Chatwin, 2009; Pryor, 1999). Several techniques for augmenting airway clearance have been developed independently during the years, with the goal of improving lung mechanics and gas exchange, and preventing atelectasis and infections. The techniques and the clinical use differ between physiotherapists across the world and the intensity, duration and frequency have changed during the years. Different maneuvers, including special breathing techniques, manual techniques and postural drainage, and the therapeutic use of special devices, masks and valves have been described. (van der Schans et al., 1999).

Physiotherapy assessment of airway clearance is to a less degree dependent on the specific medical diagnose, but rather focuses on deficiencies at physiological and functional levels (Gosselink et al., 2008). In chronic pulmonary diseases (as cystic fibrosis, primary ciliary dyskinesia, bronchiectasis and chronic obstructive pulmonary disease), airway clearance is reduced due to impairment of the mucociliary escalator (Finder, 2010), contrasting

neuromuscular diseases, where ineffective cough due to respiratory muscle weakness is the major concern (Chatwin, 2009). Effectiveness of airway clearance in persons with neuromuscular diseases has been shown to be related to enhancement of PCF (Bach, Ishikawa & Kim, 1997; Bach & Saporito, 1996; Dohna-Schwake et al., 2006; Bach, 1994). Techniques augmenting cough and increasing PCF are recommended to prevent and treat chest infections. Assisted cough techniques improve the deep inspiration and / or expiration, and aims to increase the expiratory airflow during the expiratory phase of cough. (Gosselink et al., 2008; Bott et al., 2009; Anderson, Hasney & Beaumont, 2005).

2.2. The larynx

2.2.1. Function and anatomy

The larynx is a valve to the airways and has three main tasks; it is controlling airflow during respiration, protecting the lungs from aspiration, and plays a key role in phonation. Reflexes and involuntary activity controls the protective tasks, but functions of speech and respiration are initiated voluntarily but regulated involuntarily. The larynx extends from the tip of the epiglottis, through the vocal folds and beneath the border of the cricoid cartilage. The larynx consists of muscles for adduction and abduction, ligaments and rigid cartilage skeletons. The laryngeal muscles are both under voluntary and involuntary control (reflex control of muscles). (Pierce & Worsnop, 1999). The larynx is innervated by the internal branch of the superior laryngeal nerve and the recurrent laryngeal nerves; both branches of the vagus nerve (Schweizer & Dorfl, 1997). See Figure 1 for lateral and top views of the larynx. Larynx is considered to mature through puberty and little is known regarding inter individual variability throughout adult life in healthy individuals.

Abduction of the glottis is fundamental for allowing air flow in and out from the lungs during respiration. The main muscle in the larynx capable of performing abduction is the Posterior Crico-Arytenoid (PCA) muscle. The PCA muscle has a phasic relationship with the diaphragm, which suggests that when the diaphragmatic stimulation is increased, the PCA activity increases in a coordinated manner, creating an increased laryngeal abduction. (Brancatisano, Dodd & Engel, 1984).

During normal quiet breathing, the glottis widens during inspiration and narrows during expiration. This widening occurs ahead of the onset of inspiration, whereas the narrowing begins before the onset of expiration. A progressive narrowing during the full range of expiration has been observed at rest in normal subjects. (Brancatisano, Collett & Engel, 1983; England, Bartlett & Daubenspeck, 1982).

Both forced inspiration and expiration are associated with pronounced activation of the intrinsic laryngeal muscles (Kuna & Vanoye, 1994). When ventilation is increased, as in response to hypercapnia or to exercise, the narrowing of the glottis during expiration decreases (England & Bartlett, 1982; England, Bartlett & Knuth, 1982; Beaty, Wilson & Smith, 1999). During forced expiration maneuvers, narrowing of the vocal folds has been observed. Both the PCA muscle and laryngeal adductor muscles activate during forced expiratory maneuver. (Kuna & Vanoye, 1994).

Adduction of glottis is important both in speech and during the effort closure, such as Valsalva maneuver (Lumb, 2009 ; Bartlett, 1989). Effort closure is a tight occlusion of the vocal folds which is required to perform expulsive effort as in coughing. During swallowing effort closure is combined with lifting of the larynx and elevating the epiglottis to avoid the food bolus to entire the airways. (Lumb, 2009).

Mechanically applied pressure ventilation influences the conditions in the larynx. Activity of the PCA muscle has been shown to disappear during passive hyperventilation (Kuna, McCarthy & Smickley, 1993). Passive progressive positive pressure ventilation results in progressive glottic narrowing in healthy awake subjects. Progressive glottic narrowing occurs especially in the absence of diaphragmatic activity. (Jounieaux et al., 1995). This may implicate that the phasic relationship between the diaphragm and PCA muscle operates also during positive pressure ventilation. The glottic narrowing during positive pressure ventilation increases the inspiratory resistance and reduces progressively the fraction of delivered minute ventilation reaching the lungs (Jounieaux et al., 1995).

Applied negative pressures in healthy subjects has been demonstrated to provoke partial or total narrowing of the upper airway at the pharyngeal and the oropharyngeal level and a decrease of the expiratory flow due to this. (Suratt, Wilhoit & Cooper, 1984; Sanna et al., 1994; Younes et al., 1994).

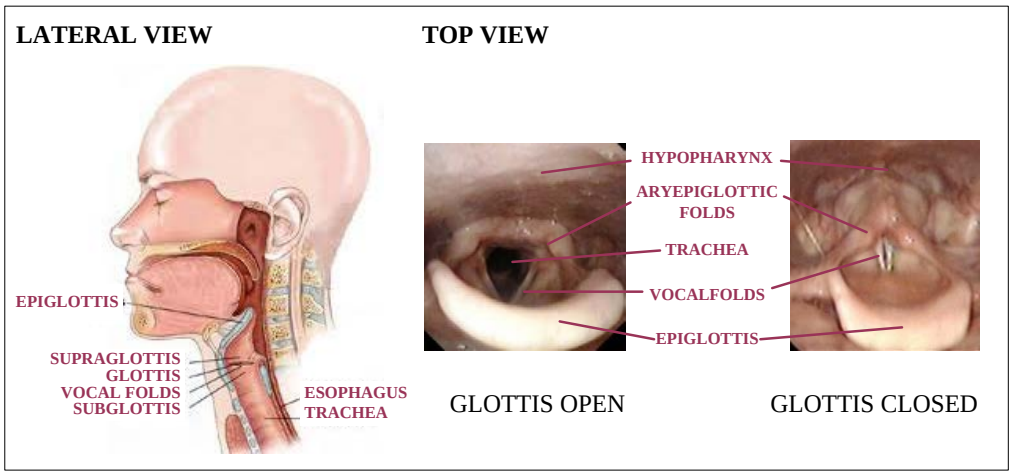


Figure 1 Lateral and top view of the larynx, and positions of closed and open glottis. Illustration used in lateral view is modified from (Center for Advanced Head & Neck Surgery, 2012).

2.2.2. Aerodynamics in the larynx

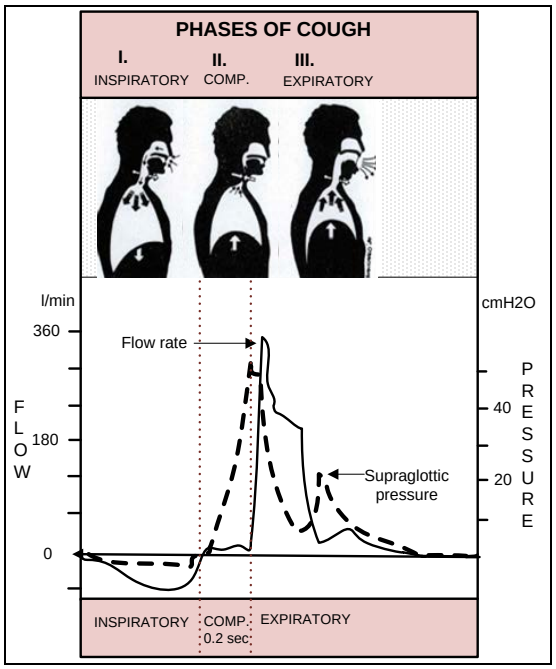
The type of flow, either laminar or turbulent, contributes to flow resistance of the airways; turbulent flow generates more resistance than laminar flow. Most of the turbulent airflow is shown to be located in central airways. Thereby, at higher flow rates, the laryngeal resistance becomes proportionally larger than resistance in the lower airways. (Ferris, Mead & Opie, 1964).

The pressure gradients at the laryngeal entrance are influenced by increased flow, a phenomenon explained by aero dynamical principle of Bernoulli and the Venturi effect. The Bernoulli principle may be described as follows: as a fluid (or a gas) passes a point which is narrowing or widening, both velocity and pressure of fluid (gas) will vary; decreasing lumen increases the flow and decrease the pressure. The Venturi effect is a jet effect where a positive pressure through a small lumen will not only decrease the pressure according to Bernoulli, but also generate a negative pressure. In the larynx, this generated negative pressure may suck the structures of pharynx inwards. (Fajdiga, 2005).

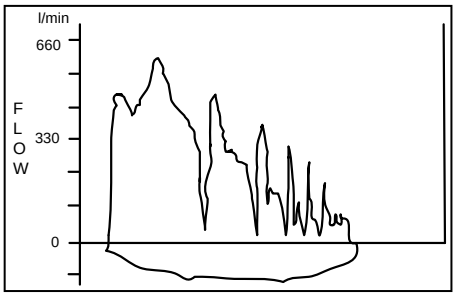
The Bernoulli principle and the Venturi effect at the laryngeal inlet has also been suggested e.g. to influence the condition known as floppy epiglottis during Continuous Positive Airway Pressure (CPAP) therapy, in which the epiglottis is sucked into the laryngeal inlet during inspiration with positive pressure (Shimohata et al., 2011).

2.3. Cough

Cough is an important defense mechanism of the airways (Sivasothy et al., 2001 ; Widdicombe, 1989), removing airway secretions from the central airways and protecting against chest infections (Chatwin et al., 2003; Bach, Ishikawa & Kim, 1997). The airways contain irritant sensors, which get triggered by chemical or physical irritants in the tracheobronchial three, subsequently producing a cough. A cough is a centrally organized complex event, and may be started both by reflexes or voluntary (Leith, 1985). A normal cough consists of several phases: 1) inspiration, 2) compression and 3) expiration (Hardy & Anderson, 1996; Holinger & Sanders, 1991; McCool, 2006; Leith, 1977). In the first phase, the vocal folds abduct and the inspiratory muscles attain insufflation of air up to 85 – 90 % of total lung capacity. Inspiration is followed by a short hold and thereafter the compressive phase of cough in form of a rapid and firm closure of the glottis for 0.2 seconds ensued by vigorous expiratory effort. Intrathoracic pressure during glottic closure can be as high as 400 cmH_2O. In the finale phase, the vocal cords abduct and the glottis opens abruptly while contraction of expiratory (abdominal and intercostal) muscles generate a high expiratory flow rate, typically with peak cough flow (PCF) of 360–1200 l/min. (Leith, 1977; McCool, 2006). See the Figure 2. During the final expulsive phase, releasing pressures shear the secretions from the airway walls and move secretions upwards. Short series of glottis closures, each with compressive and expulsive phases, may interrupt the expiration phase. This can be seen as a series of "cough spikes" on a maximal expiratory flow volume curve. (Chaudri et al., 2002). See the Figure 3.



←**Figure 2 I. Inspiration II. Compression and III. Expiration phases of cough due to generated flows and supraglottic pressure. Modified from (Leith, 1977 ; McCool, 2006).**



↑**Figure 3 Prospective "cough spikes": flow transients on the flow-volume loop. Modified from (Chaudri et al., 2002).**

2.3.1. Normal cough at the level of the larynx

During cough, complex and coordinated laryngeal movements are crucial for establishment of high expiratory flow, which can remove airway secretions from the airways. At the level of larynx each cough consists of three distinct parts: 1) an opening phase, 2) a closing phase and 3) a secondary opening of the vocal folds. The first opening movement of the arytenoid cartilages and vocal folds facilitates the deep inspiration in preparation for the expected cough. The deep inspiration is followed by a rapid and firm adduction of the vocal folds together with the act of the Aryepiglottic muscles and their continuation (the Oblique and Transverse Arytenoids muscles). The effect of this maneuver is to close the inlet of larynx by bringing the aryepiglottic folds tight together. This firm closure enables the larynx to withstand the high pressures that can be generated in the thorax. This closed phase lasts much longer than during ordinary phonation. When the supraglottic pressure reaches a certain level, the resistance of the laryngeal adductors is ultimately overcome and the glottis opens. Expulsion of air is seen as a single opening of the vocal folds or as repetitive closures. (von Leden & Isshiki, 1965; Bartlett, 1989; Britton et al., 2012).

2.3.2. Peak Cough Flow

Peak cough flow (PCF) measures the highest expiratory flow during coughing and can determine one's ability and (indirectly) strength to cough. (Chatwin, 2009). It is performed by encouraging the subject to take a deep inspiratory breath and then actively cough via a mask or a mouthpiece into to a peak flow meter (Chatwin & Simonds, 2009; Sancho et al., 2004a). Normal values of PCF in adults are >360 l/min (Leiner et al., 1963; McCool, 2006). A minimum assisted PCF of >160 l/min is required to clear airway secretions in patients who have difficulties in clearing secretions due to respiratory muscle weakness (Bach, Ishikawa & Kim, 1997; Bach, 1995; Bach et al., 1993). Current recommendations advocate the use of MI-E in NMD when Peak Cough Flow <160 l/min as an alternative or supplement to other cough augmentation techniques (Anderson, Hasney & Beaumont, 2005).

2.3.3. Weak ability to cough

A wide variety of NMD may result in compromised pulmonary function. Despite pathophysiology, these diseases may evolve a common clinical picture of pulmonary complications while disease is progressing. Weak ability to cough is central in the clinical picture of NMD. (O'Donnell, 2000). Weakness in respiratory muscles causes a reduction in the available airway pressure to perform an effective cough maneuver. This leads to impaired ability to cough effectively in persons with NMD and thereby problems with airway secretions (Mustfa et al., 2003). See Figure 4 demonstrating relationships of the pathologies leading to pulmonary complications in neuromuscular disorders (NMD).

In addition to measurement of PCF, pulmonary function measurements may be used to assess lung function, per se the strength of the respiratory muscles, and to assess control of the glottis in persons with NMD. Symptoms and signs related to respiratory muscle failure are of great importance. Evaluation of respiratory muscle strength is easily performed by measuring maximal inspiratory (PI_{max}) and expiratory (PE_{max}) mouth pressure (Ringqvist, 1966; Black & Hyatt, 1969). PI_{max} and PE_{max} values have a wide distribution, but lower limits of normal (5% percentil) are in defined males as < 80 cmH_2O and in females < 70 cmH_2O (Troosters, Gosselink & Decramer, 2005). PE_{max} below 45 cmH_2O may indicate a compromised ability to cough. (Perez, 2006).

Persons with NMD can be further weakened during acute viral illness, which has been demonstrated to reduce vital capacity (VC) due to the reduced inspiratory and expiratory muscle strength (Poponick et al., 1997). On this basis, PCF of 270 l/min has been identified as a cutoff point for initiating assisted cough techniques (Bach, Ishikawa & Kim, 1997).

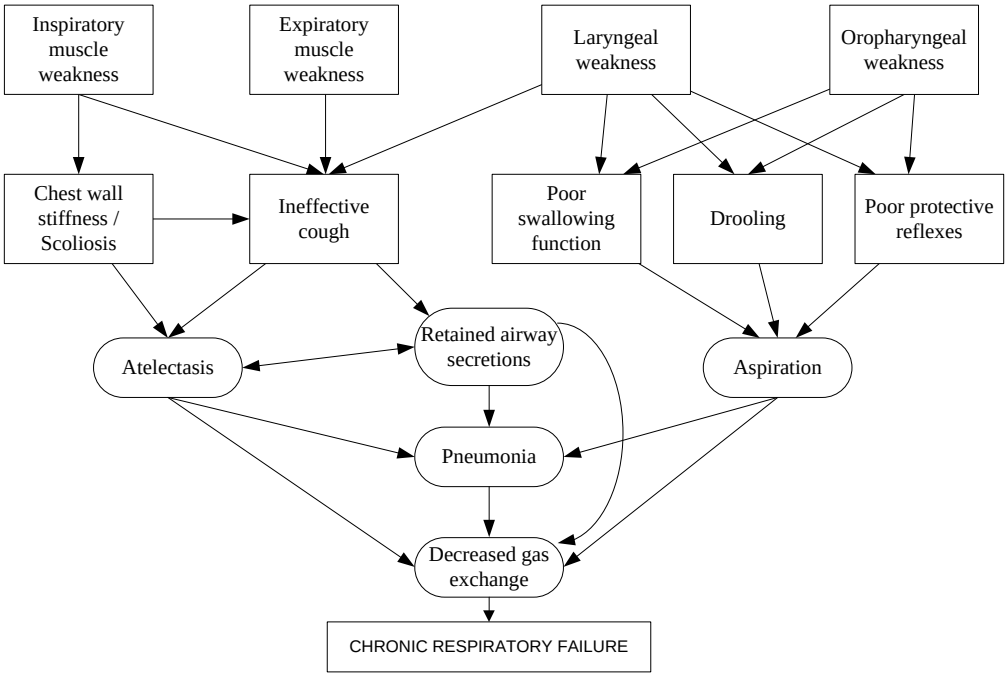


Figure 4 Pathologic relationships leading to pulmonary complications in persons with neuromuscular diseases. Modified from *(O'Donnell, 2000)*.

2.4. Mechanical insufflation-exsufflation (MI-E)

A mechanical cough device using the technique of MI-E, delivers a deep inspiration (insufflation) of the lungs followed immediately by deep expiration (exsufflation) of the lungs, by applying sequentially positive and negative pressure swings. The rapid switch from the positive to the negative pressure aim to simulate the airflow changes that occurs during a normal cough, potentially assisting secretion clearance (Homnick, 2007). Theoretically, MI-E mechanically compensates both weak inspiratory and expiratory capacity. The insufflation aims to "fill" the lungs and the exsufflation aims to "empty" the lungs of air. A voluntary maneuver of cough is desired when using MI-E, and patients

must learn to co-ordinate their own cough (glottis closure) when the device switches from insufflation to exsufflation. (Chatwin, 2008). Without the effort of glottic closure, MI-E assists expiration instead of cough.

The effect of MI-E is mainly associated with increased PCF and thereby potentially augmenting airway clearance (Chatwin et al., 2003; Chatwin & Simonds, 2009; Fauroux et al., 2008; Hanayama, Ishikawa & Bach, 1997; Miske et al., 2004; Sancho et al., 2004b; Winck et al., 2004; Sivasothy et al., 2001; Bach, 1994; 1993; Mustfa et al., 2003; Pillastrini et al., 2006). The use of a mechanical cough device with the technique of MI-E has been shown to be the most effective physiotherapeutic approach for increasing PCF and maintaining vital capacity in persons with neuromuscular diseases (Bach, 1993; Bach et al., 1993; Chatwin et al., 2003; Anderson, Hasney & Beaumont, 2005; Mustfa et al., 2003; Bach, 1995). Treatment is tolerated by most patients with neuromuscular diseases, and it is a safe method for removing airway secretions (Barach & Beck, 1954; Miske et al., 2004; Bach, 2002: p.154-155; 1993; Barach, 1955; Williams & Holaday, 1955; Fauroux et al., 2008; Chatwin et al., 2003).

2.4.1. MI-E devices

The most commonly used MI-E device in Norway is Cough Assist® (Respironics, Murrysville, USA) (Andersen, Tollefsen & Fondenes, 2011). Other devices on the market include Pegaso® (Dima Italia, Bologna, Italy) and Nippy Clearway® (B&D Electromedical, Warwickshire, UK). A tubing kit connects the device to the patient. It consists of a bacterial filter, a tube, an adapter and an interface. Interfaces used non-invasively are either a facemask or a mouthpiece. (Chatwin, 2008). See Figure 5.

Figure 5 Devices on the market for mechanical insufflation-exsufflation: Cough Assist® with a tubing kit, Pegaso® and Nippy Clearway®

2.4.2. Clinical use of MI-E device

MI-E has been used in our hospital (Haukeland University Hospital, Bergen, Norway) since 2001 both with inpatients and in home treatment schedules. Assessment of the ability to cough and clear airway secretions is routinely performed by physiotherapists. The role of the physiotherapist in the treatment with MI-E is central; to evaluate the individual need for MI-E, to implement MI-E and to evaluate effects of MI-E and the patient response, to guide the patient in training with MI-E, titrate the settings of MI-E, perform daily treatments and train the caregivers and other health care workers how to use MI-E in the hospital and / or in home setting.

In clinical use, there is no simple algorithm or one setting that suits all patients. Both titrating the settings and the clinical use of MI-E is always done based on individual assessment. Physiotherapists use MI-E with indication to both the lung recruitment and to assist cough as a part of the total respiratory physiotherapy treatment. It is important to build up to a good chest expansion and adjust the negative pressure until the audible quality of the cough has improved. MI-E is often combined with manually assisted cough. (Chatwin, 2008). See Figure 6.

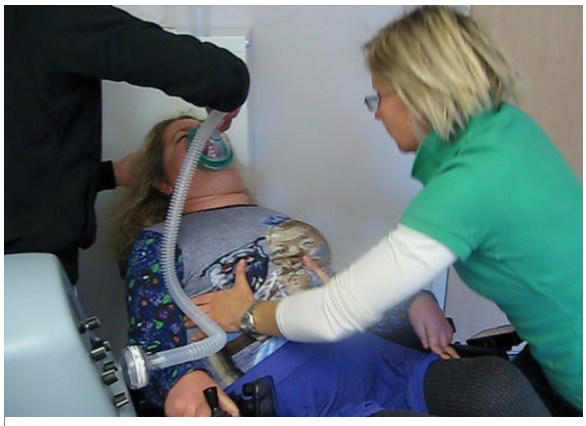


Figure 6 MI-E in combination with manually assisted cough (photo presented with permission from the patient)

The daily treatment at home is usually performed by the personal caregivers according to individually tailored routine procedures for the home use. A fixed procedure is established also in research settings. This contrasts the clinical use of MI-E in respiratory physiotherapy, which most often is a dynamic process including also patient interaction. Nevertheless, a simplified treatment with MI-E can shortly be described as follows:

MI-E devices can be operated in manual or automatic mode, depending on the model. Setting of the device entails adjustment of the positive and negative pressure (cmH_2O) in the inspiratory and expiratory phase respectively, the inspiratory flow rate (l/min) and the duration of the insufflation, exsufflation and the short pause between exsufflation and next insufflation (seconds). One treatment with MI-E usually consists of several phases of

coughing and rest. One phase involves up to five cycles of insufflations and exsufflations after each other, followed by 30 seconds of rest. An additional thoracoabdominal thrust applied by the therapist or an assistant can be provided during exsufflation. These cycling periods are repeated several times or until secretions are substantially expelled. (Homnick, 2007).

2.4.3. Settings

The literature varies regarding the settings of the inspiratory and expiratory pressures, ranging from 20 to 60 cmH_2O in positive and negative pressures. (Chatwin, 2009; Homnick, 2007). Initially the MI-E device is set up to deliver pressures tolerated by the patient and to produce an effective cough. High pressures of ±60 cmH_2O are described and used by Bach and co-workers (Bach et al., 1993; Bach, 1993; 1994; Bach et al., 2002; Bach, Niranjan & Weaver, 2000; Tzeng & Bach, 2000). However, good applying lower pressures are reported by other researches; ±30 cmH_2O (Miske et al., 2004) and +20 cmH_2O to -30 cmH_2O (Chatwin et al., 2003; Vianello et al., 2005). Pressure settings of ±40 cmH_2O seem to be a good compromise between efficacy and comfort (Senent et al., 2011; Sancho et al., 2003; Sivasothy et al., 2001; Homnick, 2007). Higher pressures may become necessary when lung mechanics change during the illness (Sancho et al., 2004c).

A study by Faurox et al. (2008) highlighted the inaccuracy between pressure settings on the device and the pressures measured in the facemask. Pressures were shown to be significantly lower in the mask (Fauroux et al., 2008). This may indicate that that therapists should not be too anxious about high pressure settings on the device (Chatwin, 2009).

Knowledge regarding optimal time settings for the phase of insufflation, exsufflation and subsequent pause is mainly experience based. Time settings should be titrated for both patient comfort and with the goal of achieving a deep inspiration and thereby having enough time to cough up secretions. (Chatwin, 2008). A bench study by Gomez-Merino et al. demonstrated that increasing the insufflation time is more important for optimal PCF that increasing the exsufflation time (Gomez-Merino et al., 2002).

The inspiratory flow can be adjusted to 10 or 3 l/min (Chatwin, 2008). Lower inspiratory flow is rarely used clinically and most often in cases where patients subjective experience the inspiration to bee "too intense".

2.4.4. Instructions

Clinical instructions, used by therapists during MI-E have not been studied, but it is described that the therapist should indicate when insufflation commences and the patient should coordinate their cough when the MI-E device switches to exsufflation (Pryor, Prasad & Chatwin, 2008; Chatwin, 2008).

Instructions on how to perform a task are widely used as a therapeutic strategy to help the patient to perform functional tasks. Cognitive processes are important for the movements and motor control. The nature of the tasks determines the type of movements required. Motor control of movements includes both the perception and the action systems that must be organized to achieve the specific goals to perform a task. Constraints related to tasks can impose constraints on the neural organization of the movement. In the case of disease or damage on the central neural system, this will influence the individual development of movement pattern to meet the demands of the task. In the therapeutic context, both the guidance and consideration into underlying impairments are important to maximize the functional independence. (Shumway-Cook & Woollacott, 2007 p.5). If clinical instructions therapists use to guide the patient during MI-E treatment, have any influence on movements in larynx, either to keep laryngeal entrance open or to the enhancement of PCF, is yet to be studied.

2.5. Laryngeal pathology of possible conditions limiting the effect of MI-E

Several neurological conditions can disrupt a persons laryngeal function, e.g. sensory impairment, motor weakness, abnormal reflexes or poor coordination (Woodson, 2008). A bulbar dysfunction presents as weakness of pharyngeal muscles, spasticity or lack of coordination of laryngeal or lingual muscles (Hillel et al., 1999; Carpenter, McDonald & Howard, 1978).

Opening and closure of the glottis require intrinsic laryngeal muscle contractions involving complex neural interactions that are partly not understood (Hardy & Anderson, 1996; Holinger & Sanders, 1991). Laryngeal weakness may lead to upper airway collapse during expiration, and even during inspiration (Bach, 2003). Bulbar dysfunction may lead to abnormal cough and therefore non-invasive secretion management may become ineffective (Lechtzin, 2006; Shneerson & Simonds, 2002; Cazzolli & Oppenheimer, 1996; Aboussouan et al., 1997).

Sancho et al. (2004b) performed an effect study with MI-E in both bulbar and non-bulbar ALS patients. Study found that some ALS patients with bulbar dysfunction failed to reach PCF values >160 l/min with MI-E. This study also visualized pharyngeal and oropharyngeal structures during MI-E with CT scanning at baseline and during exsufflation with pressure of -40cmH_2O in three ALS patients from the total study sample of 26 subjects. Patients were instructed to try to keep their airway open, but otherwise remain passive. Their study found variable degrees of closure of the nasopharynx with retraction of the uvula and reduction of the lateral diameter of pharynx during the exsufflation cycle. The narrowing was most severe at the level of oropharynx. The authors concluded that inability to close the glottis may cause laryngeal narrowing and reduced expiratory flow during negative pressure with MI-E. Consequently the MI-E failed to assist the patient reach adequate PCF. (Sancho et al., 2004b).

Research in the field of MI-E and intrinsic laryngeal weakness is lacking and to my knowledge the study of Sancho et al. (2004b) is the only one which has examined the obstruction of the upper airway during MI-E. Their study has limitations, but is to date the best available research in this field. Other researchers have based their conclusions on assumptions. Bach (2003) assumed that upper airway collapse may occur during MI-E and that this treatment therefore is totally ineffective. Kang and Bach have suggested that ALS patients with bulbar dysfunction would alternatively benefit from a single deep insufflation delivered by the device, combined with a manually assisted cough (Bach, 2003; Kang & Bach, 2000). These assumptions are based on clinical experience, not on evidence based knowledge.

Existing knowledge from the study of Sancho et al (2004b), assumptions from other authors and my own clinical experience support the hypothesis that coordinated closure

and opening of the glottis is crucial to the effectiveness of MI-E. Nevertheless, movements and patency at the laryngeal level during MI-E are yet to be studied.

2.6. Methodological background

The following will briefly describe the methodological background to investigate a new phenomenon.

2.6.1. Systematic description of a new phenomenon

When there is a lack of knowledge about a specific topic, identification and description of the phenomenon is required (Polit & Beck, 2008: p.19). The nature of the research question defines the type of research method required. Both qualitative and quantitative research methods can be used. Qualitative studies focus on the essence of the phenomena and the view is highly subjective in form of the perception of the researcher. The researcher is more interested in the process than in the product, and does not manipulate the variables. Qualitative research emphasizes induction, whereas quantitative research emphasizes deduction. Quantitative research often gathers data through laboratory settings and by using instrumentation, whereas a qualitative researcher is the primary instrument of the data collection and in analyze of the data. (Thomas & Nelson, 1990: p.322).

To map out a new phenomenon, an observational descriptive research design can be used in an early phase; simply by observing the subjects and by using qualitative and quantitative analysis of the observations. Quantitative descriptive research involves several study designs, as survey, cross-sectional-, cohort- and case studies. (Thomas & Nelson, 1990: p.263 & 286; Polit & Beck, 2008).

Primarily the observations must be systematic to be scientific. Systematic observations can be structured or unstructured, depending on if observations are done with or without explicit predefined categories. (Polit & Beck, 2008: p.433). According to Thomas & Nelson (1990) the basic considerations in observational research are: What behaviors (events) and what subjects will be observed? Where, when and how many observations will be made? How will the observations be scored and evaluated? (Thomas & Nelson, 1990: p.287).

When the phenomenon is unknown, researchers will in the initial phase primarily observe to establish a preliminary understanding of the phenomenon. Over time, researches become more active as participants and observations become to take more focus. Observations tend to range from descriptive observations (broad observations) to focused observations (more carefully selected events) and eventually to selective observations designed to facilitate comparisons. (Polit & Beck, 2008: p.411).

A category system in observational design represents an attempt to state qualitative behavior and events in the observational setting in a systematic fashion. A careful and explicit definition of the observed behavior and characteristics are critical for development of a good category system. Each category must be explained carefully. Checklists based on the category system are tools for recording the occurrence or frequency of predestinated behavior, events or characteristics. (Polit & Beck, 2008: p.433-434 & 446). When the features are clearly defined, the tallying, or frequency counting method, can be applied to quantitate the findings (Thomas & Nelson, 1990: p.289).

2.6.2. Quality of the measurements

Measurement is an integrated part of research documentation and thereby measurement quality is a necessary component in all research. When developing a new method to measure, this issue is of great concern. Quality of the measurements can be evaluated with using the concepts of reliability and validity. A measure with great errors has little utility or meaning, and it is unreliable. A reliable measure is valid if it is repeatable and the information it provides is meaningful. (Domholdt, 2005 p.265 & 274). Measurement validity indicates to what extent the test or instrument measures what it is supposed to measure (Thomas & Nelson, 1990: p.343), and thereby validity refers to whether a study is able to scientifically answer the research questions it is designed to answer (Domholdt, 2005: p.259). Validity is an important consideration since it refers to the soundness of the interpretation of a test. (Thomas & Nelson, 1990: p.343).

The measure is considered reliable if it gives us the same result repeatedly; assuming that what we are measuring is not changing. Due to classical measurement theory every measurement or score consists of both a true and an error component, and thereby the "r*eliability is the degree to which test scores are free from errors of measurement"*

(Domholdt, 2005: p.255). Since the true score for the measurement is unknown, the relationship between repeated measures is used to estimate the error of the measurement. Reliability can be assessed in two ways: relative or absolute reliability. Relative reliability examines the relationships between two or more sets of repeated measures, and the absolute reliability examines the variability of the scores from measurement to measurement. (Domholdt, 2005: p.257). Interrater reliability examines if the test is repeatable and provides the same results irrespective of who carries out the measurement. Intrarater reliability assess if the test results are the same when assessed twice or more by the same observer. Intrasubject reliability defines if the test provides the same results if carried out twice or more in the same subject under the same conditions. (Domholdt, 2005: p.257).

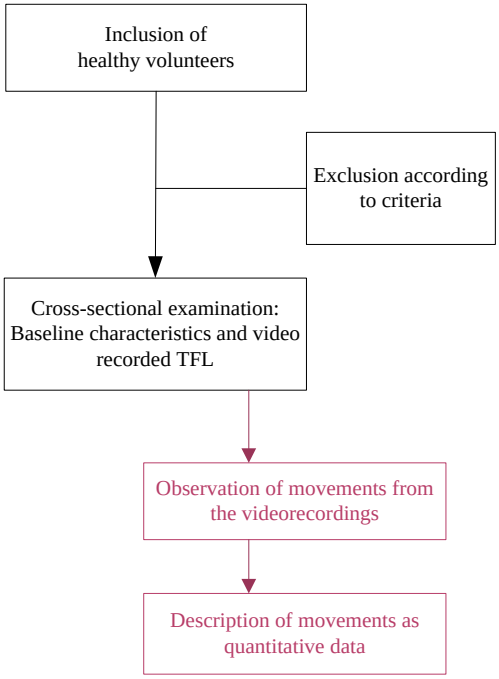
In addition to validity and reliability, sensitivity and specificity are important in an evaluation tool. The sensitivity of a test assess the percentage of the individuals with a particular diagnosis who are correctly identified as positive by the test, and the specificity is assessed with the percentage of individuals without the particular diagnosis who are correctly identified as negative by a test (Domholdt, 2005: p.559-560).

3. MATERIAL AND METHODS

3.1. Design

A descriptive cross-sectional observational study design will be used to obtain the aims of the study. Healthy individuals will be examined for laryngeal movements during MI-E with different pressure settings and clinical instructions at one point in time. See the Figure 7 for flow-chart of the study design.

Since the phenomenon under study is undescribed, this initial pilot study will focus on observation and description of the phenomenon of laryngeal movements during the application of MI-E in healthy subjects (Polit & Beck, 2008: p.411). As with other forms of quantitative descriptive research, a sufficient number of subjects and observations per subject will have to be obtained in order to have adequate internal and external validity (Thomas & Nelson, 1990: p.291). A cross-sectional study documents the status of a group at a particular point in time and it allows for documentation of the nature of the phenomenon through a systematic collection and description of data (Domholdt, 2005: p.198).



TFL = Transnasal fiberoptic laryngoscopy

Figure 7 Study design

3.2. Subjects

This pilot study included healthy volunteers. Twenty (20) medical students, eight males and twelve females, were recruited. A convenience sampling method (Polit & Beck, 2008 p.341) was used; medical 3.rd and 4.th year students were asked to participate. Subjects received both verbal and written information about the study, and a consent statement was signed (Appendix 1: “Informert samtykke for friske deltagere”). Prior to inclusion, all participants were screened for the criteria for exclusion. Exclusion criteria were age < 18 years, a history of laryngospasm, presence of tracheostomy, any lung disease, cancer or acute chest infection one month prior to the study and mentally instability. Upon inclusion subjects were informed how the data was saved and stored.

3.3. Sample size

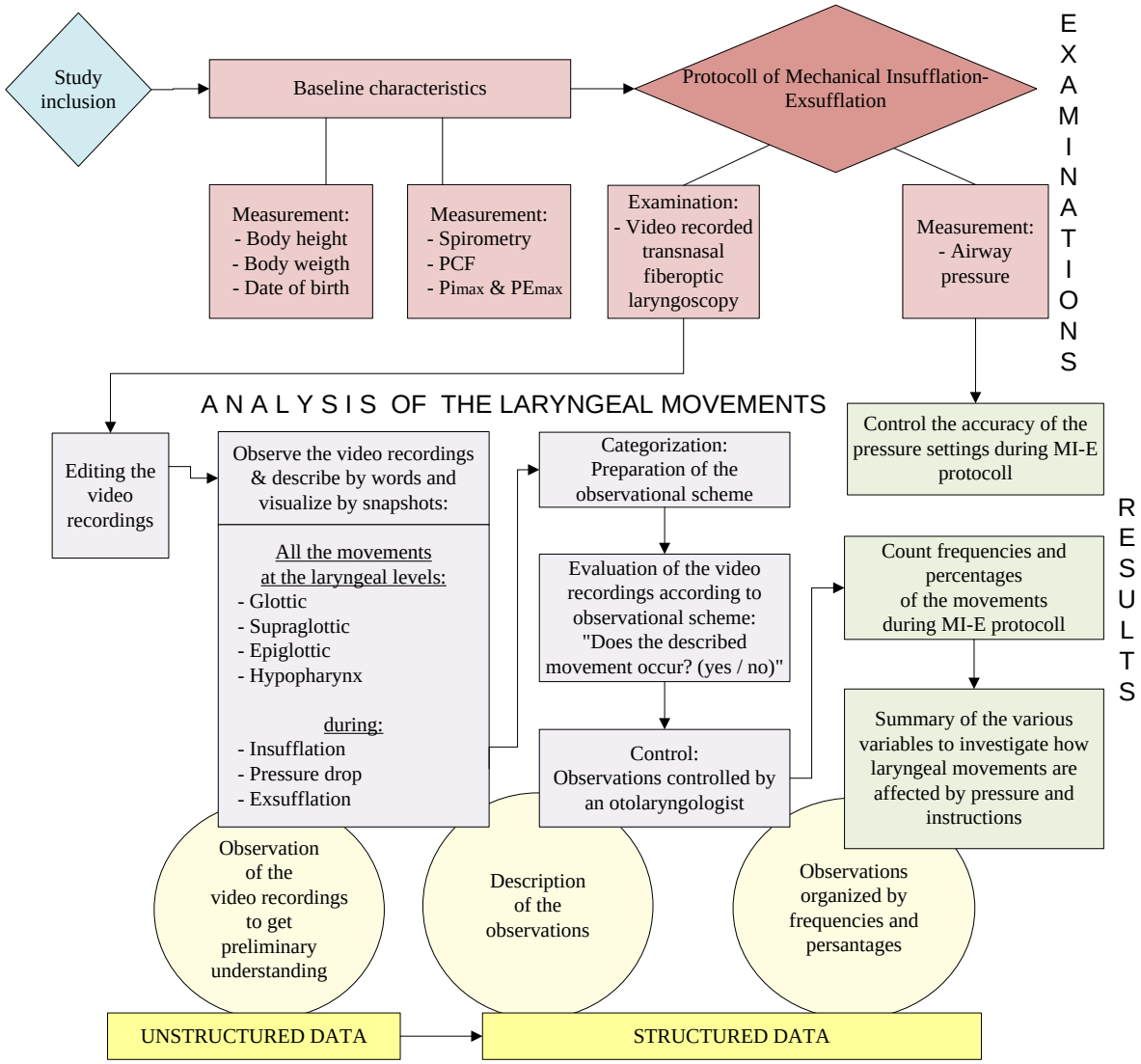
There is no algorithm to calculate how large a sample size was needed for this study. The power of a study is an expression of the probability to detect a predefined difference between groups when it exists. Power calculations requires that same estimate of the distribution of the measure of interest is available and also that same information is at hand, suggesting what differences that is of clinical interest. Power tables or programs can be used to determine the needed sample size to achieve a particular level of power in quantitative studies. Earlier studies or a pilot study can allow the researcher to estimate within-group values. (Domholdt, 2005: p. 298). Since there was no previous information on which to base the estimates, I did not perform a formal power calculation. Nevertheless the present study has no intention in generalizing the results. However, planned correlations between selective observations require a certain sample size. As this study was performed within a master study context a sample size of twenty was chosen. Healthy individuals are expected to be a homogeneous group and thereby this small sample may be adequate. (Polit & Beck, 2008: p.350).

3.4. Test procedures

Examination of the healthy volunteers included:

- Measurement of pulmonary function and assessment of respiratory strength.
- Video recorded examination with TFL during MI-E intervention.
- Registration of airway pressure during the MI-E intervention.

See Figure 8; a flowchart describing all examinations used in this study and how the TFL examination led to results by analyzing laryngeal movements from the video recordings.



PCF = Peak cough flow, Pi_{max} = Maximal inspiratory mouth pressure, Pe_{max} = Maximal expiratory mouth pressure, MI-E = Mechanical insufflation-exsufflation

Figure 8 Flowchart of the examinations and analysis of the observations

3.4.1. Examination of pulmonary function

An examination of pulmonary function in the present study determines population demographic characteristics. Pulmonary function tests and evaluation of the respiratory strength was performed prior to the examination of larynx during MI-E.

Spirometry was performed seated. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and peak expiratory flow (PEF) were recorded, with values expressed as percentages of predicted. Spirometry was measured with a Vmax 22 (SensorMedics, Yorba Linda, USA), applying quality criteria according to the guidelines of The European Respiratory Society (Quanjer et al., 1993). PCF was measured with a hand held peak flow meter (Vitalograph, Ennis, Ireland). Respiratory muscle strength, both as Pi_{max} and Pe_{max}, were measured in a seated position (Wilson et al., 1984) using respiratory pressure meter Micro RPM (Micro Medical Ltd, Rochester, England), which give the plateau value of the measurement. The highest value in three or more attempts was recorded. In measurements with existing reference values, results were expressed as percentages of the predicted value.

3.4.2. Transnasal fiberoptic laryngoscopy examination

Laryngoscopic examination was in this study used to visualize laryngeal movements and patency during the use of MI-E in healthy volunteers. Intervention with MI-E during laryngoscopy is described in chapter 3.5. Observations were made in a laboratory setting and participants were well informed that their laryngeal structures were visualized and filmed with TFL during the intervention with MI-E.

Transnasal fiberoptic laryngoscopy (TLF) examination allows for a direct visualization of the larynx and has made possible to the description of the circumstances inside in the larynx. Transnasal laryngoscopy examination is "the gold standard" for diagnosis of vocal cord dysfunction (VCD) with visualization of abnormal larynx movement (Morris et al., 1999; Beaty, Wilson & Smith, 1999; Christopher et al., 1983; McFadden & Zawadski, 1996).

Videotape is an invaluable instrument in observational design. Video recordings can be replayed as often as needed during evaluation, facilitating observation of fine and rapid

movements. In addition both the analysis and categorization can be done after the examination. (Thomas & Nelson, 1990: p.290 & 380; Polit & Beck, 2008: p.433).

Preparations and implementation

Subjects were examined one at a time. The medical doctor, the physiotherapist (me) and the chief of the test laboratory were present during the examination. A pulmonologist was present during the examination of the first subject.

Participants were verbally informed about the examination. Regular nasal spray (Rhinox®) was used to facilitate the introduction of the laryngoscope. In addition, local anesthesia was applied as a nasal spray (Xylocain®) before the examination. TLF examination was performed by a medical doctor. When the nasal septum was adequately anesthetized, the flexible laryngoscope (Olympus ENF-P3, Tokyo, Japan), diameter 4,5 mm, lubricated with local anesthesia gel (Xylocain®) was lead through the nose and via the nasopharynx to visualize the larynx. A modified oronasal facemask (UltraClear anesthetic face mask, Armstrong Medical, Coleraine, Northern Ireland) served to secure the laryngoscope and allowed for the use of MI-E via a mask. The laryngoscope was attached to the headmount with scope holder (custom made). The laryngoscope was connected to the video camera system (Telecam, Karl Storz, Tuttlingen, Germany) for continuous recording of laryngeal movements during the entire examination.

To ensure adequate technical quality of the recordings, the larynx was visualized on a television screen during the entire procedure. See Figures 9A and 9C. The use of MI-E with a standardized protocol of settings was performed during video recorded examination with transnasal fiberoptic laryngoscopy, see figure 9B. Each examination was filmed by two continuous video recordings:

- By an endoscopic video camera system from the fiberoptic transnasal laryngoscopy, situated above the epiglottis.
- By an external video camera with a microphone, to document the Cough Assist® control panel showing the phases of insufflation and exsufflation with a manometer.

Figure 9 A) Flexible laryngoscope was lead via the nose and nasopharynx by a medical doctor. B) MI-E was used while the larynx was visualized during the entire procedure on a television screen and video recorded for further evaluation of laryngeal response pattern. C) Examination was recorded with two continuous videos on the same screen, showing synchronously the laryngeal view and the phases of MI-E on the device.

Editing the video recordings

The video recordings from each subject was edited to a new video file including 12 film clips based on a representative shots from each time frame (Table 1) of each intervention arm (Table 2). One representative shot included the whole insufflation-exsufflation cycle or the insufflation-spontaneous cough cycle. See Table 1 for definitions for onsets and offsets of the time frames of MI-E for editing and evaluation.

A total of 20 videos, consisting of 239 film clips from 20 subjects were edited. The video recording of one subject could not be reviewed in full because of a technical failure. Thereby the last intervention arm (ie. applied mechanical insufflation with +50cmH_2O combined with manually assisted cough during voluntary cough) was edited and evaluated for 19 persons only. The same person performed all the editing.

Table 1 Definitions for onsets and offsets of phases for insufflation, pressure drop, exsufflation and voluntary cough with no applied negative pressures

Phase of interest	Definition for onset	Definition for offset
Insufflation (Time settings for insufflation is 2 sec)	The point when the positive pressure is started with the MI-E device. Observed from the manometer on the control panel of the MI-E device.	Offsets when the positive pressure on manometer turns off.
Pressure drop (Automatically very rapid phase)	The point when the MI-E device switches from positive to negative pressure. Observed from the manometer on the control panel of the MI-E device.	Offsets when the negative pressure is achieved on the manometer on MI-E devices control panel.
Exsufflation (Time settings for exsufflation is 2 sec)	The point when the negative pressure is applied with the MI-E device. Observed from the manometer on the control panel of the MI-E device.	Offsets when the negative pressure on manometer turns off.
Voluntary cough with no applied negative pressures	The point when the MI-E device has pressure of zero after an insufflation. Observed from the manometer on the control panel of the MI-E device.	Offsets when the last glottic closure in voluntary cough maneuver is observed.

Analysis of the laryngeal movements from the video recordings

Since the laryngeal movements during MI-E have not been studied / evaluated previously, there was no standardized assessment score available to use in this study. The intention of analyzing of the video recordings was to establish a scientific foundation and a tool for the assessment of the larynx during MI-E in patients. An observer in this study was me; the physiotherapist performing the study. I cooperated with an otolaryngologist who also trained me to understand the anatomy of the larynx.

The video recordings displayed a top view of the larynx: the base of the tongue, the hypopharyngeal space, the epiglottis, the aryepiglottic folds and the vocal folds. The time frame of interest in observations and in the evaluation was defined as the whole cycle of MI-E: the insufflation with positive pressure, the pressure drop form positive to negative (when the device switches from insufflation to exsufflation) and the exsufflation with negative pressure or voluntary cough combined with a manually assisted cough. See Table 1. Such explicit definitions are critical for a good category system (Polit & Beck, 2008: p.433).

Video recordings were replayed as many times as needed both in real time and in slow motion. By doing so we could generate structured data from the unstructured data by recording all the observed movements during the applied MI-E cycles. The observed movements were described both by words (as adductive and abductive movements of the vocal and aryepiglottic folds, retroflex movement of the epiglottis, hypopharyngeal constriction or backward movement of the base of the tongue), and with snapshots of laryngeal positions during the movements. Thereby observed movements were categorized to explicitly defined categories (same as defined phases of interest, see Table 1.). Thereafter an observation scheme was prepared. This was a checklist, based on categorized movements. See the appendix 2: "Observasjonsskjema". This process of analyzing the video recordings made unstructured observations into structured observations (Polit & Beck, 2008: p.405).

Thereafter all the video recordings were reviewed and evaluated again both in real time and in slow motion: all the observed movements at the laryngeal level in each subject were assessed and related to an individual observation scheme (described movement occurs: yes

/ no). Quantitative categorical data were gathered by counting the frequencies of described movements in the sample (Thomas & Nelson, 1990: p.289).

Thereafter an otolaryngologist checked the assessment of the observations according to observational scheme and video recordings. The otolaryngologist also assessed the anatomy of the larynx during breathing in all subjects from the video recordings.

I invited a group of specialists to a meeting to get advice to establish a scoring system with continuous variables (Domholdt, 2005: p.246). This group included senior and junior otolaryngologists, a speech therapist, a pulmonary physician, a physiotherapist who were specialist in exercise induced laryngeal obstruction, and myself. There was an agreement within the group to not develop an assessment score based on findings from healthy individuals. This decision was based on the reflections that we must first examine patients and observe their laryngeal response pattern, to be able to develop a scoring system that can be clinically useful. A score system based on normal findings alone will most likely not be valid with real patients, according to responsiveness to change (Domholdt, 2005: p.261).

3.4.3. Measurement of airway pressure during intervention with MI-E

Synchronized with the visual representation of the larynx, a measurement of airway pressure was recorded in nine of a total twenty (9 of 20) subjects. Airway pressure measurements provided information about whether pressures agree with pressures delivered from the MI-E device.

A pneumotachograph (Hans Rudolf Linear Pneumotach 0-800 LPM; Hans Rudolph, Inc.; Kansas City, USA) was placed between the facemask and the tube to the Cough Assist®, to measure pressures during intervention with MI-E. Signals were digitalized and sampled for analysis (MP100; Biopac Systems, Goleta, USA) and run on a computer with appropriate software (Acqknowledge; Acqknowledge Software; East Palo Alto, USA). A similar set up of measurements of airway pressure, flow and volume was also used in the study of Faurox et al. to analyze the physiological effects and tolerance of MI-E in children with neuromuscular diseases (Fauroux et al., 2008).

3.5. Intervention with MI-E

Intervention was performed according to a standardized MI-E protocol applying 12 different conditions (intervention arms) with increasing pressure settings, different verbal instructions, and with or without thoracic thrust. See Table 2. The protocol was prepared according to what is commonly used during therapeutic trials in neuromuscular patients with a manifest cough problem.

Cough Assist® (Respironics, Murrysville, USA), device for MI-E, was used with standardized settings of time: insufflation time of two seconds, exsufflation time of two seconds and pause time (between exsufflation and next insufflation) of one second. Pressures of ± 20, 30, 40 and 50 cmH_20 were used. A positive pressure was always indicated with an instruction to inhale. With the onset of each negative pressure the participant was instructed both to actively exhale and cough during the exsufflation. Thereafter, a single mechanical insufflation (MI) was applied using the same positive pressures followed by voluntary cough (without applying negative pressures) and manually assisted with a thoracic thrust. Since secretions can interrupt the quality of the video images, each intervention arm (MI-E cycles) was repeated three to five times to ensure optimal quality of recordings. The same skilled physiotherapist (me) instructed all subjects, operated the Cough Assist® device, delivered manually assisted coughs and adjusted the pressure settings during the examination.

Table 2 Standardized protocol of conditions during the intervention with MI-E with the increasing pressure settings, the different instructions and the application of manually assisted cough during intervention with MI-E and MI.

CLINICAL INTERVENTION WITH COUGH ASSIST®:					
Intervention arm	**Pressure settings (cmH_2O)**		**Instruction during exsufflation**		**Manually assisted cough**
	MI-E	**MI**	**Active exhale**	**Active cough**	
1.	±20		x		
2.	±20			X	
3.		+20		X	x
4.	±30		x		
5.	±30			X	
6.		+30		X	x
7.	±40		x		
8.	±40			X	
9.		+40		X	x
10.	±50		x		
11.	±50			X	
12.		+50		X	x

Intervention arms 1.-12. With respective pressures of MI-E or MI combined with instruction to either actively exhale or cough during exsufflation. Additional manually assisted cough was provided in combination with MI. MI-E=Mechanical insufflation-exsufflation, MI=Mechanical insufflation.

3.6. Statistical analysis

Application to The Data Inspectorate in Helse-Vest IKT for approval for obtaining data and to establish a data register was sent in November 23rd 2011 and approved on February 6th 2012.

Data from the examinations were stored in separate registration forms, where participants were allocated a participant number. Data was therefore anonymized, and stored and later processed in Excel for Windows Office version 2010 (Microsoft, Redmond, Washington, USA) and in SPSS (Statistical Package for Social Sciences, SPSS Inc, Chicago, Illinois, USA) for Windows version 17.0 for statistical processing. SPSS and Excel were used for analyses.

Baseline characteristics are presented as descriptive statistics in tables with means, ranges and standard deviations. Quantitative data of laryngeal movements during the MI-E are presented as frequencies and percentages, both in tables and histograms. To explore relationships between selected observations the Chi-square test was used with categorical variables and the Fisher's exact test when excepted values in any group were <5. Data from the measurements of airway pressure during MI-E intervention is presented as descriptive statistics with mean, range and standard deviations in tables and in a figure. The level of statistical significance was set as $p<0.05$. Two-sided p-values were used.

3.7. Ethical aspects

Ethical considerations in this study were based on the Declaration of Helsinki (Rickham, 1964).

Healthy adults were examined using a Cough Assist®, a device for MI-E designed for airway clearance treatment of persons with reduced ability to cough due to neuromuscular weakness. Pressure settings and clinical instructions used in this study were based on established clinical use of MI-E in our hospital with real patients. The positive and negative pressures used during the test procedure with MI-E were planned to be increased gradually, as this give the test subject time to get familiar to the feeling of the in-exsufflations.

The test procedures of this study were considered safe, with minimal risk to healthy subjects without pulmonary problems. Fiberoptic laryngoscopy through the nose is an intervention that does not require sedation and that skilled hands can perform with little discomfort and no risk. An integrated set-up with fiberoptic transnasal laryngoscopy examination has been used in our hospital in diagnosis of exercise induced upper airway flow limitation both in children and adults. It is well tolerated and easy to perform. (Heimdal et al., 2006; Maat et al., 2009; Røksund et al., 2009).

The study was based on voluntary participation and the subjects could withdraw from the study at any time. Participants were asked to sign a written consent form. Information was treated anonymously. A list of names with subject numbers was stored separately from the data and saved in accordance with the advice from Norsk Samfunnsvitenskapelig Datatjeneste AS (NSD).

Application to The Regional Committee for Medical Research Ethics for approval to perform the study was sent on March 22nd 2011 (Appendix 3: "Søknad til Regional Etisk Komite om prosjektgodkjenning"), and an approval was received on May 6th 2011 (Appendix 4: "Informasjon om vedtak").

4. RESULTS

4.1. Baseline characteristics

4.1.1. Sample, pulmonary function and the assessment of respiratory strength

All of the recruited healthy volunteers n=20, eight (8) males and twelve (12) females, successfully completed the examination with the MI-E protocol. Mean (range) age was 24 (21 - 29) years. Mean (range) FVC was mean 106.7 (90 to 121) % of predicted, mean (range) FEV1 was 99.1 (71 to 121) % of predicted and mean (range) PEF was 102.2 (78 to 130) % of predicted. PCF, Pi_{max} and Pe_{max} were normal in all subjects, i.e. PCF > 360 l/min (Leiner et al., 1963), and Pi_{max} and Pe_{max} > 70 cmH_2O in females and > 80 cmH_2O in males (Troosters, Gosselink & Decramer, 2005). Descriptive data of the sample demographics is presented in Table 3.

Table 3 Sample demographic data (n=20)

Variable	Mean	SD	Min	Max
Age, years (n=20)	24.4	1.875	21.0	29.0
Female (n=12)	24.4	2.020	22.0	29.0
Male (n=8)	24.3	1.767	21.0	26.0
BMI, kg/cm^2 (n=20)	22.6	1.976	19.8	26.3
Female (n=12)	22.0	2.020	19.8	26.1
Male (n=8)	23.4	1.655	21.8	26.3
FVC, % of predicted (n=20)	106.7	8.498	90.0	121.0
Female (n=12)	106.0	9.496	90.0	117.0
Male (n=8)	107.7	7.226	99.0	121.0
FEV1, % of predicted (n=20)	99.1	12.995	71.0	121.0
Female (n=12)	99.9	14.003	71.0	119.0
Male (n=8)	98.0	12.154	79.0	120.0
PEF, % of predicted (n=20)	102.2	15.643	78.0	130.0
Female (n=12)	101.4	16.080	78.0	127.0
Male (n=8)	103.5	16.080	80.0	130.0
PCF, l/min (n=20)	501.0	100.651	340.0	670.0
Female (n=12)	439.1	67.515	340.0	550.0
Male (n=8)	593.7	62.835	500.0	670.0
Pi_{max}, cmH_2O (n=20)	101.0	26.866	53.0	173.0
Female (n=12)	92.08	21.694	53.0	135.0
Male (n=8)	114.3	29.645	89.0	173.0
Pe_{max}, cmH_2O (n=20)	132.6	28.331	88.0	199.0
Female (n=12)	122.1	22.176	88.0	159.0
Male (n=8)	148.3	30.575	108.0	199.0

SD=standard deviation, BMI=Body mass index, FVC=forced vital capacity, FEV1=forced expiratory volume in 1 second, PEF=peak expiratory flow, PCF=peak cough flow, Pi_{max}=maximal inspiratory mouth pressure, Pe_{max}=maximal expiratory mouth pressure

4.1.2. Anatomy of the larynx in the sample

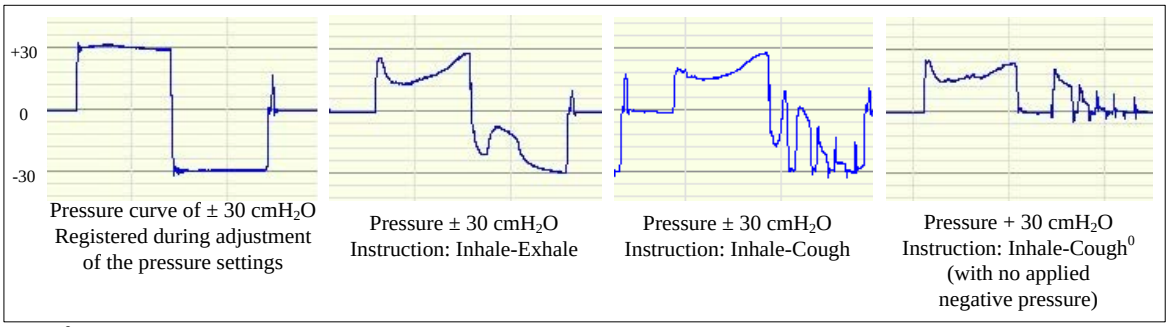
4.2.3. Movements during exsufflation and movements during voluntary cough with no applied negative pressures

In all subjects, regardless of the applied negative pressures and given instructions, the vocal folds abducted in the beginning of the phase of both cough and expiration, and both with or without applied negative pressures during mechanical exsufflation. Although infrequently after the initial opening of the vocal folds, a variety of movements were observed.

Sequential glottic closures

Cough presented as sequential (repetitive) glottic closures (cough spikes), in the majority of the subjects when instructed to cough. A range of one to six cough spikes were observed during the time frame of cough, and a range of one to three were observed during the time frame of exhale. An example of cough spikes is presented as a graph of one subjects airway pressure registration in Figure 13.

When instructed to exhale with exsufflation sequential vocal fold closures were observed in 1 of 20 subjects at -20 cmH_2O, in 2 of 20 subjects at -30 cmH_2O, in 5 of 20 subjects at -40 cmH_2O and in 3 of 20 subjects at -50 cmH_2O. When instructed to cough with applied exsufflation sequential glottis closures were observed in 15 of 20 subjects at -20 cmH_2O, in 16 of 20 subjects at -30 cmH_2O, in 14 of 20 subjects at -40 cmH_2O and in 17 of 20 subjects at -50 cmH_2O. When instructed to cough with no applied negative pressure, sequential glottis closures were observed in 15 of 20 subjects after insufflation of +20 cmH_2O, in 14 of 20 subjects after insufflation of +30 cmH_2O, in 14 of 20 subjects after insufflation of +40 cmH_2O and in 1 of 19 subjects after insufflation of +50 cmH_2O insufflation.



Cough^0= Cough with no applied negative pressures

Figure 13 Pressure curves. Registered from the pressure adjustment og ±30 cmH_2O on the MI-E device, and from one subjects examination, illustrating cough spikes during the time frame of cough during exsufflation and cough with no applied negative pressure.

Subsequent narrowing of the vocal folds

A gradual narrowing of the vocal folds was observed after the initial opening of the vocal folds both after instruction to exhale and to cough. This was predominantly during the high negative exsufflation pressures of -40 and -50 cmH_2O. A progressive narrowing of the vocal folds during the time frame of cough was also observed in combination with sequential glottic closures.

Abduction and adduction of the aryepiglottic folds

Both when instructed to cough and exhale during exsufflation with and without application of negative pressures, abductive as well as adductive movements of the aryepiglottic folds were observed. Generally, an initial abduction was followed by an adduction.

Constriction of the hypopharyngeal space

Hypopharyngeal constriction was observed most frequently during exsufflation when instructed to cough. The subjects with observed hypopharyngeal constriction could have a relatively pronounced reduction of the hypopharyngeal space.

When instructed to exhale during exsufflation, hypopharyngeal constriction was observed in 3 of 20 subjects at -20 cmH_2O, in 6 of 20 subjects at -30 cmH_2O, in 9 of 20 subjects at -40 cmH_2O and in 11 of 20 subjects at -50 cmH_2O. When instructed to cough with exsufflation, a hypopharyngeal constriction was observed in 9 of 20 subjects at -20 cmH_2O, in 7 of 20 subjects at -30 cmH_2O, in 10 of 20 subjects at -40 cmH_2O and in 15 of 20 subjects at -50 cmH_2O. When instructed to cough, with no applied negative pressure, a hypopharyngeal constriction was observed in 5 of 20 subjects after insufflation of +20 cmH_2O, in 7 of 20 subjects after insufflation of +30 cmH_2O, in 6 of 20 subjects after insufflation of +40 cmH_2O and in 11 of 19 subjects after insufflation of +50 cmH_2O.

Frequencies of all laryngeal movements observed during exsufflation are presented in Table 7 and in Figure14. Frequencies of laryngeal movements observed during cough with no negative pressures during exsufflation are presented in Table 8 and in Figure 15.

Table 7 Frequencies of laryngeal movements observed during mechanical exsufflation phase according to applied negative pressures and instructions. Figures are numbers with positive findings (% of sample), n=20.

Intervention		Movements observed during the exsufflation of 2 seconds					
		Glottic		Supraglottic		Epiglottic	Hypopha-ryngeal
Negative pressure (cm H_2O)	Instruction	Initial abduction of the vocal folds	Subsequent narrowing of the vocal folds	Abduction of the aryepiglottic folds	Adduction of the aryepiglottic folds	Retroflex movement of the epiglottis	Hypopharyngeal constriction
-20	Inhale-Exhale during exsufflation	100 %	40 %	85 %	30 %	20 %	15 %
	Inhale-Cough during exsufflation	100 %	30 %	80 %	80 %	20 %	45 %
-30	Inhale-Exhale during exsufflation	100 %	50 %	80 %	45 %	25 %	30 %
	Inhale-Cough during exsufflation	100 %	35 %	85 %	75 %	25 %	35 %
-40	Inhale-Exhale during exsufflation	100 %	70 %	65 %	60 %	25 %	45 %
	Inhale-Cough during exsufflation	100 %	60 %	70 %	80 %	20 %	50 %
-50	Inhale-Exhale during exsufflation	100 %	65 %	75 %	50 %	35 %	55 %
	Inhale-Cough during exsufflation	100 %	60 %	75 %	95 %	20 %	75 %

Table 8 Frequencies of laryngeal movements observed during voluntary cough (combined with manually assisted cough) with no applied negative pressures, according to applied positive pressures and instructions. Figures are numbers with positive findings (% of sample), n=20 unless stated otherwise.

Intervention		Movements observed during the cough without applied exsufflation					
		Glottic		Supraglottic		Epiglottic	Hypopha-ryngeal
Positive pressure during insufflation (cm H_2O)	Instruction	Initial abduction of the vocal folds	Subsequent narrowing of the vocal folds	Abduction of the aryepiglottic folds	Adduction of the aryepiglottic folds	Retroflex movement of the epiglottis	Hypopharyngeal constriction
0	Inhale at +20 cmH_2O -$Cough^0$ without exsufflation	100 %	35 %	80 %	75 %	15 %	25 %
	Inhale at +30 cmH_2O -$Cough^0$ without exsufflation	100 %	35 %	85 %	85 %	15 %	35 %
	Inhale at +40 cmH_2O -$Cough^0$ without exsufflation	100 %	50 %	70 %	95 %	15 %	30 %
	Inhale at +50 cmH_2O -$Cough^0$ without exsufflation	100 % *	52,6 % *	68,4 % *	89,5 % *	21,1 % *	57,9 % *

$Cough^0$= Cough with no negative pressures applied. *n=19 because of a technical failure in video recordings of one subject, $Cough^0$= Cough with no negative pressures applied.

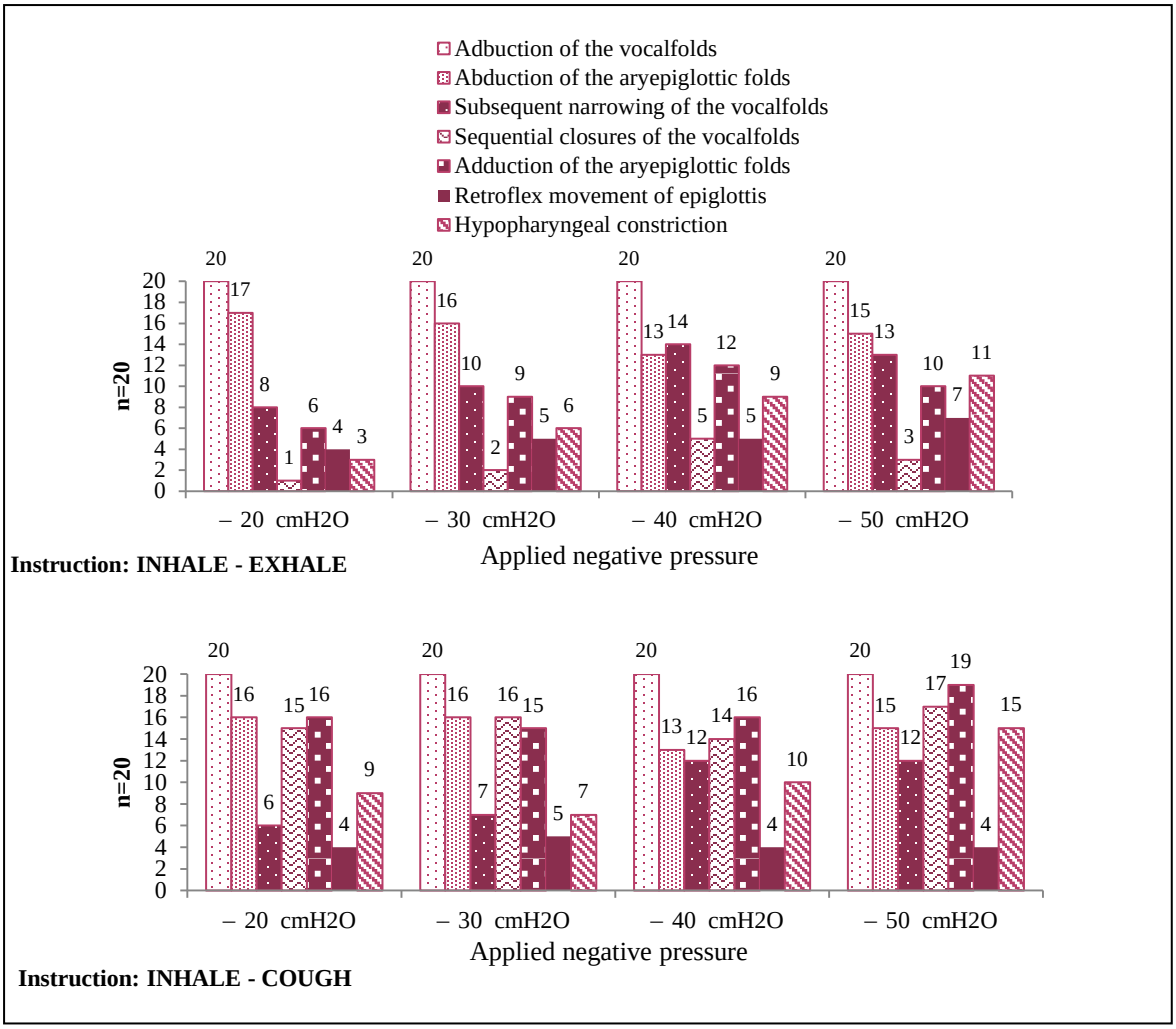
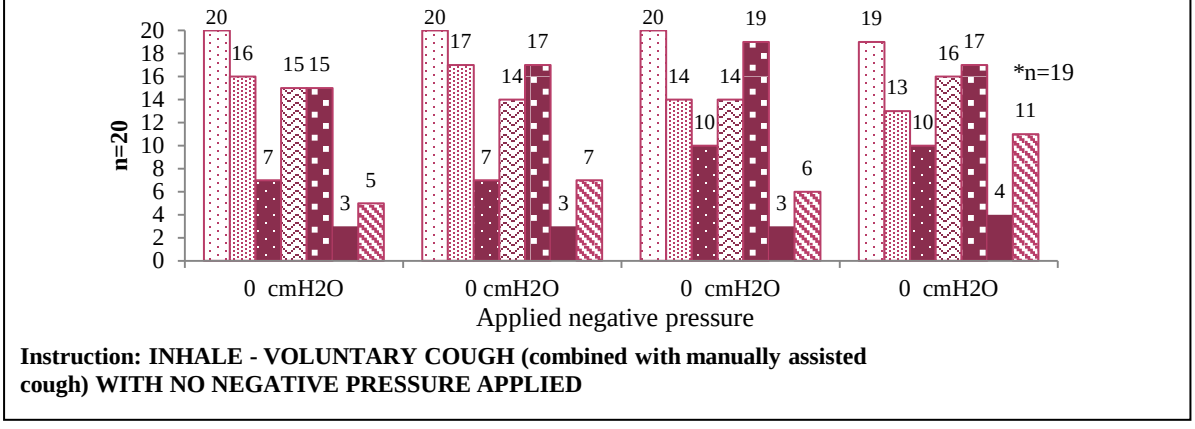


Figure 14 Histogram of laryngeal movements observed during mechanical exsufflation, n=20



*n=19 because of a technical failure in video recordings of one subject

Figure 15 Histogram of laryngeal movements observed during voluntary cough (combined with manually assisted cough), with no applied negative pressure, n=20 unless stated otherwise

4.3. Relationships between selected observations

Chi-square tests were performed to examine relationships between gender and hypopharyngeal constriction during applied exsufflation, and between anatomical differences in the epiglottis (high standing epiglottis and floppy epiglottis) and retroflex movement of the epiglottis during the intervention. Excepted values were < 5 and Fisher's tests were therefore used for computing the exact probability of Chi-square statistics.

4.3.1. Gender and hypopharyngeal constriction

The Fisher's test indicated a significant association between being male and hypopharyngeal constriction during exsufflation when instructed to cough at the pressures of -20 to -40 cmH_2O and when instructed to exhale at the pressures of -30 and -40 cmH_2O. Significant associations were also observed between being male and hypopharyngeal constriction when instructed to cough without applied negative pressure after insufflation of positive pressures of 30 to 50 cmH_2O. See Table 9.

Table 9 Relationships between being male and hypopharyngeal obstruction during active exhale and cough with exsufflation and during voluntary cough without applied negative pressures

Intervention	Male gender p
-20 Exhale	1.000
-30 Exhale	.001
-40 Exhale	.005
-50 Exhale	.197
-20 Cough	.005
-30 Cough	.004
-40 Cough	.001
-50 Cough	.055
$Cough^0$ after Inhale at +20	.347
$Cough^0$ after Inhale at +30	.004
$Cough^0$ after Inhale at +40	.018
$Cough^0$ after Inhale at +50	.003

$Cough^0$= Cough with no negative pressures applied.
p= p-value; based on Fisher's test.

4.3.2. Anatomy of the larynx and retroflex movement of the epiglottis

The Fisher's test indicated a significant relationship between anatomical high standing epiglottis and retroflex movement of the epiglottis during insufflation and partly during exsufflation, $p < .05$, but not during pressure drop, $p > .05$. See Table 10 for the overview of p values.

A significant relationship was also found between anatomical floppy epiglottis and retroflex movement of epiglottis during insufflations, $p< .05$. There was no significant

relationship between floppy epiglottis and retroflex movement of epiglottis during pressure drop or during exsufflation, p> .05. See Table 11 for the overview of the p values.

Table 10 Relationship between anatomical high standing epiglottis and retroflex movement of the epiglottis during the whole intervention

	Retroflex movement of epiglottis during:		
Intervention	**INSUFFLATION p**	**PRESSURE DROP p**	**EXSUFFLATION p**
-20 Exhale	.022	.111	.007
-30 Exhale	.000	.111	.001
-40 Exhale	.022	.111	.031
-50 Exhale	.022	.111	.022
-20 Cough	.007	.111	.101
-30 Cough	.000	.111	.001
-40 Cough	.001	.111	.007
-50 Cough	.017	.111	.101
Cough^0 after Inhale at +20	.001	.111	.031
Cough^0 after Inhale at +30	.001	.111	.031
Cough^0 after Inhale at +40	.001	.111	.031
Cough^0 after Inhale at +50	.074	.123	.117

Cough^0= Cough without exsufflation, p= p-value; based on Fisher's test

Table 11 Relationship between anatomical floppy epiglottis and retroflex movement of the epiglottis during the whole intervention

	Retroflex movement of epiglottis during		
Intervention	**INSUFFLATION p**	**PRESSURE DROP p**	**EXSUFFLATION p**
-20 Exhale	.270	1.000	.509
-30 Exhale	.049	1.000	.140
-40 Exhale	.031	1.000	.140
-50 Exhale	.031	1.000	.270
-20 Cough	.018	1.000	.509
-30 Cough	.018	1.000	.009
-40 Cough	.009	1.000	.088
-50 Cough	.074	1.000	.509
Cough^0 after Inhale at +20	.009	1.000	.404
Cough^0 after Inhale at +30	.009	1.000	.404
Cough^0 after Inhale at +40	.031	1.000	.404
Cough^0 after Inhale at +50	.546	1.000	.530

Cough^0= Cough without exsufflation, p= p-value; based on Fisher's test

4.4. Airway pressure during clinical intervention with MI-E

Airway pressures measured between the face mask and the tube from the MI-E device were constantly lower than the positive and negative pressures set on the device. This was more prominent during positive pressures (insufflations). The performance of the MI-E device was more accurate at the negative pressures due to mean values. See Tables 12 and 13, and Figures 16 and 17 for an illustrated bar graph with a plot of a range.

Table 12 Airway pressure measured by the mask in cmH_2O during mechanical insuffation (n=9)

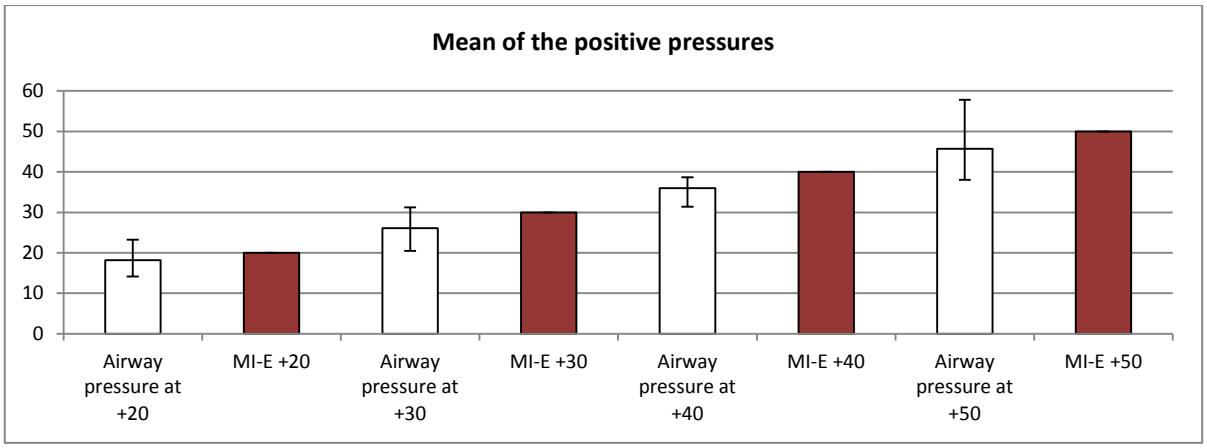
Pressures set at the device	Mean	Min	Max	SD
+ 20 cmH_2O	18.19	14.12	23.25	2.47840
+ 30 cmH_2O	26.09	20.49	31.20	2.65327
+ 40 cmH_2O	35.99	31.40	38.70	1.96757
+ 50 cmH_2O	45.74	38.04	57.79	3.95636

SD=standard deviation

Table 13 Airway pressure measured by the mask in cmH_2O during mechanical exsuffation (n=9)

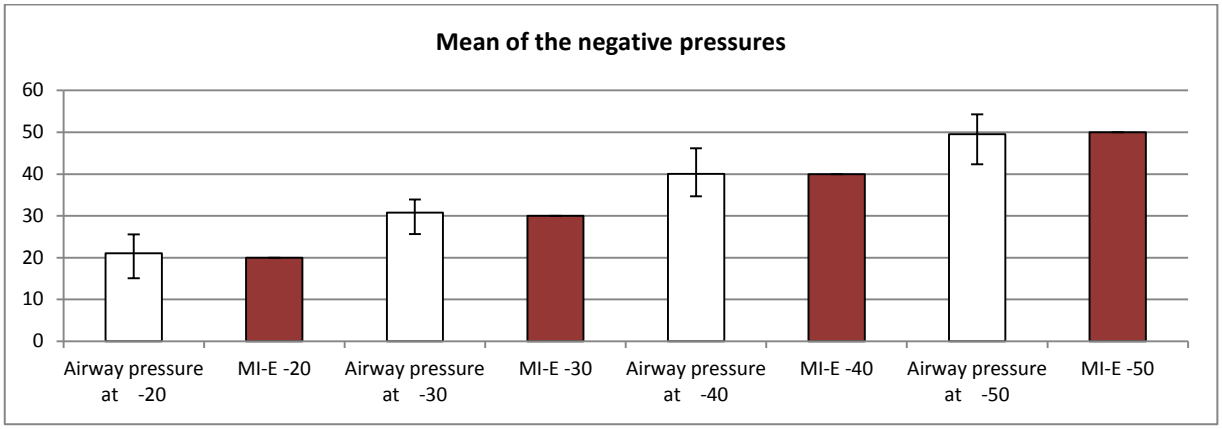
Pressures set at the device	Mean	Min	Max	SD
-20 cmH_2O	-21.07	-25.58	-15.12	3.37785
-30 cmH_2O	-30.80	-33.93	-25.68	2.68618
-40 cmH_2O	-40.05	-46.15	-34.70	2.89936
-50 cmH_2O	-49.56	-54.26	-42.33	3.22274

SD=standard deviation



MI-E = Mechanical insufflation-exsufflation

Figure 16 Bar graph with mean and plot as range illustrating difference between the airway pressure measured during intervention with MI-E (white bars) and the positive pressure settings on the MI-E device (red bars) at four pressure levels (+20 cmH_2O, +30 cmH_2O, +40 cmH_2O and +50 cmH_2O).



MI-E = Mechanical insufflation-exsufflation

Figure 17 Bar graph with mean and plot as range illustrating difference between the airway pressure measured during intervention with MI-E (white bars) and the negative pressure settings on the MI-E device (red bars) at four pressure levels (-20 cmH2O, -30 cmH2O, -40 cmH2O and -50 cmH2O).

5. DISCUSSION

This study show that video recorded transnasal fiberoptic laryngoscopy is possible, feasible and well tolerated during MI-E in healthy subjects, and that laryngeal movements throughout the MI-E protocol may be described and characterized. The laryngeal response patterns to cough with MI-E in healthy subjects were as described for normal cough i.e. three distinct phases at the laryngeal level: an opening phase during insufflation, a closing phase during the pressure drop and a secondary opening of the vocal folds during exsufflation. When the study subjects were instructed to exhale after inhalation, most healthy subjects managed to keep the laryngeal entrance open despite the pressure drop. This indicates that healthy subjects are able to coordinate the glottic closure and opening during all phases of MI-E, which is considered crucial for its effect.

5.1. Visualization of the larynx with TFL during MI-E

All volunteers successfully completed the examination with the MI-E protocol, which indicates that the method of TFL is safe and well-tolerated during the MI-E procedure in healthy subjects.

Examination with TFL allows for direct visualization of the larynx and it is "the gold standard" for diagnosis of abnormal laryngeal anatomy and movements (Beaty, Wilson & Smith, 1999; Christopher et al., 1983; McFadden & Zawadski, 1996; Morris et al., 1999). To my knowledge, no studies have been published using TFL during MI-E.

Visualization of the larynx with TFL did provide a good overview of the larynx on the television screen. The quality of the video recordings was good and it was possible to observe movements of the laryngeal structures throughout the complete MI-E intervention. Both the laryngeal images and the pressure swings could be evaluated in a synchronized fashion since the examinations were recorded with two continuous videos running in parallel, showing the laryngeal structures and the pressure settings on the same screen.

The video recordings were invaluable as both the analysis and the categorization could be done after the examination, videotapes could be replayed as often as needed, fine nuances and rapid movements could be visualized during slow motion and the findings could be

validated afterwards by other observers. (Thomas & Nelson, 1990: p.290 & 380; Polit & Beck, 2008: p.433).

However, the examination had also some challenges. The larynx moved upwards with cough during exsufflation, which required adjustments of the position of the laryngoscope in order to follow the movements of the larynx. The movement of the laryngoscope or / and larynx during cough could interrupt video quality. The examined subjects had only small amount of airway secretions, but still secretions could block the camera and lead to poor quality of the video recordings. Particular anatomical characteristics, such as a high standing epiglottis, could prevent visual access, as experienced with one subject. Due to this, some interventions had to be repeated.

5.2. Discussion of the results

The chapter of results is extensive, and it provides a thorough description of the laryngeal response pattern to MI-E. Since the phenomenon is new and the laryngeal movements during MI-E have not been evaluated earlier, an objective presentation of the manifold is therefore considered to be necessary.

5.2.1. Subjects

The subjects were healthy volunteers as regards general health, pulmonary function, PCF and respiratory strength. No laryngeal pathology was observed at baseline in any of the participants.

All subjects were young adults and therefor the sample does not match the age of ALS patients. This may be a weakness of the study in relation to comparisons with ALS patients. However, studies that have addressed the issue of laryngeal maturation in adults do not suggest large alterations during this age span.

The gender distribution of the study was relatively balanced; 40 % were males and 60 % were females. An even more equal distribution of gender would have been preferable particularly since a significant association between male gender and hypopharyngeal constriction during exsufflation was observed.

5.2.2. Laryngeal response to insufflation

All the healthy subjects opened the vocal folds during insufflation and allowed the MI-E device to insufflate the lungs. Thereafter, a variety of other movements were observed during the time frame of insufflation.

Some studies have examined laryngeal responses to various forms of positive pressure assistance; however the laryngeal response pattern to insufflation such as in MI-E has not been examined. Positive pressure ventilation is usually associated with a passive patient with absent of inspiratory effort. Even in healthy subjects the activity of the PCA muscle has been shown to disappear during passive hyperventilation (Kuna, McCarthy & Smickley, 1993). Jounieaux et al. (1995) demonstrated positive pressure ventilation to influence the conditions in larynx in healthy awake subjects, mainly as a progressive glottic narrowing.

Sancho et al. (2004b) examined the circumstances in pharynx during exsufflation only, whereas the present study examined the laryngeal response during the whole cycle of MI-E. Both results from this study and other studies examining the larynx during applied positive pressures, indicates that the insufflation cycle is an important issue to investigate. (Kuna, McCarthy & Smickley, 1993; Jounieaux et al., 1995).

In the present study after an initial opening of the vocal folds, a subsequent narrowing of the vocal folds as well as an adduction of the aryepiglottic folds was observed in some subjects at high insufflation pressures, even if actively inhaling. These adductive movements may be seen as a reflective response of the larynx; protecting the airways from high positive pressures (Pierce & Worsnop, 1999). This may indicate that the initial abductive movements are voluntary according to the task of inhalation, but influenced by a subsequent reflex activity, promoting adduction. Narrowing of the glottis during insufflation may alternatively be due to the Bernouli principle and the Venturi effect; i.e., increasing positive pressures induce increasing airflow through a narrow tube and thereby an increased negative pressure (Fajdiga, 2005). Jounieaux et al. (1995) has shown that this glottic narrowing during insufflation may increase the inspiratory resistance and thereby progressively reduce the fraction of the air-volume that is delivered to the lungs per unit of time.

There seemed to be a relationship between retroflex movement of the epiglottis and some anatomical particularities: the results indicate that a high standing epiglottis or a floppy epiglottis may be related to a retroflex movement of this structure when a positive pressure is applied during insufflations. Seven subjects had a high standing epiglottis, indicating that this phenomenon may be common.

A floppy epiglottis has been shown in the study of Shimohata et al. (2011) to be pressed into the laryngeal inlet during inspiration during CPAP treatment. Researchers explained the phenomenon with the Bernoulli principle and the Venturi effect and laryngeal aerodynamics; a decreasing lumen increases the flow and thereby decrease the luminal pressure (Fajdiga, 2005). MI-E is used with considerably higher pressures than Shimohata et al. (2011) used with CPAP therapy; 4-7 cmH_2O. High insufflation pressures may make the Bernoulli principle in the larynx even more relevant with MI-E therapy than with CPAP. Adduction of the vocal folds and the aryepiglottic folds as well as hypopharyngeal narrowing, retroflex movement of the epiglottis and a backward movement of the tongue may all be factors that contribute to a decrease of the hypopharyngeal and laryngeal lumen which in turn will decrease the intraluminal pressure and thereby further aggravate the situation.

5.2.3. Laryngeal response to exsufflation

The present study shows that all subjects managed to open their vocal folds when exsufflation was applied. However, subsequently a variety of movements occurred, even more frequently than during the phases of insufflation and pressure drop.

To my knowledge the movements or the muscle activation at the laryngeal level during exsufflation has not been reported. However, there are some studies that have examined structures above the larynx during applied negative pressures.

Sancho et al. (2004b) found a closure of the nasopharynx with retraction of the uvula and a reduction of the lateral diameter of pharynx to a variable extent during an exsufflation phase of -40 cmH_2O. The narrowing was most severe at the level of oropharynx.

Another studies proposed that a negative pressure of -3 to -5 cmH_2O during expiration produces reflex activation in the Genioglossus muscle at the pharyngeal level (Tantucci et

al., 1998 ; Koulouris et al., 1995). With increasing negative pressures up to -35 cmH_2O the response of the Genioglossus muscle reflex was more pronounced. Negative pressures of -25 and -35 cmH_2O with open glottis caused more pronounced activation of the Geniglossus muscle compared to when glottis was closed. (Horner, Innes & Guz, 1993). Some studies have demonstrated decreased expiratory flow rates in parallel to partial or total narrowing of the upper airway at the pharyngeal and the oropharyngeal level during applied negative pressures (Suratt, Wilhoit & Cooper, 1984 ; Sanna et al., 1994 ; Younes et al., 1994).

In the present study, narrowing of the vocal folds and hypopharyngeal constriction seemed to be more severe with high negative pressures, but categorized to yes or no, these tendencies could not be verified statistically.

The results of present study may generate a hypothesis that subjects manages to voluntarily initiate an opening of the glottis, but then an applied negative pressure, alone or in combination with an active cough maneuver, produce reflex activity, which may lead to increased intrinsic constriction in the hypopharyngeal space.

A hypopharyngeal constriction was observed particularly when subjects were instructed to cough combined with applied negative pressure. Visually, these constrictive movements appeared to be dynamic in their nature, i.e. as if performed by a sphincter, increasing in severity when the negative pressures were increased. This may indicate a relation between negative pressures and hypopharyngeal constriction. If this phenomenon is due to muscle activity or to the aerodynamics in larynx is not known. Kuna and Vanoye (1994) reported marked activation of the intrinsic laryngeal muscles during forced expiration. Both the PCA muscle and the adductor muscles in larynx were active. Britton et al. (2012) described a squeezing of the pharyngeal walls during the expiratory phase of cough. These studies may support that hypopharyngeal constriction is related to muscle activity.

5.2.4. Laryngeal response to instructions during intervention with MI-E

My results indicate that there might be a relation between instructions and the coordination of the glottis. The response of the subjects to the instructions indicate that it is possible to control coordination of the glottis during MI-E; both keeping the glottis open when

instructed to exhale and close the glottis rapidly when instructed to cough, even within the wide range of pressures swings applied in this study. To my knowledge clinical instructions to guide the patient during MI-E treatment has not been studied, but it is described that the therapist should indicate when insufflation commences and that the patient should coordinate their cough when the MI-E device switches to exsufflation (Pryor, Prasad & Chatwin, 2008; Chatwin, 2008).

Overall, subjects seemed to manage their laryngeal movements in a functional way according to the task (instructions) they were confronted with and during the changing conditions (applied pressures) they were exposed to (Shumway-Cook & Woollacott, 2007: p.4). Only one subject out of totally twenty had difficulties to follow the instructions during the intervention arm of ± 30 cmH_2O. There may be several possible explanations to this: unacquaintedness to being in a test situation in general or to the use of the MI-E in particular, the ability of the instructor to give precise and understandable instructions or the ability of the participant to receive or respond to verbal instructions during the examination. The ability of a person to perceive and to respond to instructions may be understood within biomedical and biopsychological models, and will be influenced by the context of the examination and the relationship between the instructor and the person. The ability to perceive verbal instructions can also be influenced by disease. (Shumway-Cook & Woollacott, 2007: p.19). These issues have not been measured in this study.

Instruction to inhale during insufflation

The vocal folds abducted in all subjects during the initial phase of insufflation and the aryepiglottic folds were observed to follow the abducting movements of the vocal folds.

The abduction of the vocal folds is a normal maneuver both in the inspiratory phase of cough (von Leden & Isshiki, 1965) and during inspiration in quiet breathing (Brancatisano, Collett & Engel, 1983; England, Bartlett & Daubenspeck, 1982). These observed movements in the present study most probably reflect what normally takes place during inspiration and may be unrelated to the applied positive pressure. Opening of the glottis, initiated with instruction to inhale during insufflation, may be influenced by the phasic relationships between the PCA muscle and the diaphragm; the glottis opens prior to inspiration as described by Brancatisano, Dodd and Engel (1984).

Kuna, McCarthy and Smickley (1993) demonstrated that the activity of the PCA muscle disappear during passive hyperventilation. Jounieaux et.al (1995) showed that progressive glottic narrowing occurs during mechanically applied positive pressure ventilation, and particularly in the absence of diaphragmatic activity.

One may speculate if the findings of the present study could have been different if the subjects had been instructed to be more passive, for example instructed to “just let the air flow in your lungs". A passive approach in instruction could contribute important information regarding laryngeal movements in patients with reduced ability to active inspiration, such as in severe muscle weakness, as suggested by Sancho et al. (2004b). Instruction to actively inhale may positively influence the diaphragmatic activity and thereby also facilitate the PCA muscle due to phasic relationship between these two.

Instruction to exhale during exsufflation

My results indicate that if subjects were instructed to exhale instead of to cough, the glottis remained open regardless of the magnitude of the applied pressure drop. The subsequent narrowing of the vocal folds, which was observed after initial opening of the vocal folds both when instructed to exhale and to cough during exsufflation, corresponds to the progressive narrowing that has been described during expiration in normal subjects during forced vital capacity maneuvers (Kuna & Vanoye, 1994) and during quiet breathing (Brancatisano, Collett & Engel, 1983; England, Bartlett & Daubenspeck, 1982).

The consequences of an instruction to exhale (not to cough) during MI-E has not been described in the literature. The maneuver of exhaling during exsufflation may be similar to the technique of the forced expiratory technique (FET). FET is a widely used physiotherapeutic technique to remove secretions from the upper airways in patients with pulmonary diseases. It is considered an effective and gentle maneuver, and to be an alternative to voluntary cough maneuvers. (van der Schans et al., 1999; Pryor, 1999). My results indicate that larynx remains more open during MI-E when instructed to exhale than to cough during the negative pressures. It remains to be studied if the instruction of exhale during MI-E is functional in terms of managing to sheer the secretions and to generate sufficient expiratory airflow to expel the secretions.

However, some subjects had sequential glottic closures (cough spikes) when instructed to exhale during exsufflation. These movements were increasing with increasing negative pressures. In normal cough, these cough spikes cause more turbulent flow and may be crucial for the effect of cough, since the pressures swings and turbulence shear the secretions from the airway walls and thereby move secretions upwards (Chaudri et al., 2002). The tendency to increased numbers of cough spikes with increasing negative pressures during exsufflation suggest that the negative pressure may provoke glottic closures, even in subjects asked to exhale and not to cough when exhaling. This mechanism may be reflexive in their nature.

Instruction to cough during exsufflation

An initial opening of the vocal folds was observed in all subjects when instructed to cough during exsufflation. Cough spikes were observed in the majority when instructed to cough with or without applied negative pressure. This pattern is similar to the expiratory phase of normal cough (von Leden & Isshiki, 1965). The observed cough spikes may indicate increased shearing forces due to more turbulent flow (Chaudri et al., 2002) and may support the theory that cough is crucial for the effect of MI-E to remove airway secretions (Sancho et al., 2004b; Bach, 2003).

The instructions given may influence outcome independent of the pressures swings given by the MI-E, and thereby act as a confounding factor. The observations may be associated with a third factor, such as respiratory strength. This is supported by an increased tendency for hypopharyngeal constriction in males. Healthy males usually generate high maximal pressures (Pi_{max} and Pe_{max}); measurements that are used to determine respiratory strength (Ringqvist, 1966; Black & Hyatt, 1969). Since the subjects were instructed to actively exhale and cough, a possible explanation may be that intrinsic laryngeal adductor muscles get active and thereby somehow narrow the hypopharyngeal space.

Instruction to cough with no applied negative pressures

The laryngeal movement pattern during cough with no applied negative pressure was mainly as when instructed to cough during exsufflation.

A suggestion that a single deep insufflation delivered by the device combined with a manually assisted cough may be more beneficial to ALS patients with bulbar dysfunction has been raised, although without evidence based documentation (Bach, 2003; Kang & Bach, 2000). In this study, cough without negative pressure, cough with negative pressure and exhalation with no active cough were basically similar with respect to “infrequent movements” (see Figure 10). The impression was that there might have been less “infrequent movements” with cough with no negative pressures as compared to cough with applied negative pressures. This is an important issue to investigate further, but will require a more sensitive grading scale and more subjects.

5.3. Methodological aspects

5.3.1. Study design

Variables of pressures and instructions were manipulated through the intervention and the study was more focused on outcome than on process. These are important points supporting the choice of quantitative approach rather than qualitative study method (Thomas & Nelson, 1990: p.322). However, the choice of a quantitative design rather than a qualitative has resulted in missing qualitative aspects, such as the subjective perceptions and experiences from the participants and how components mesh together to form an entirety. On the other hand, using quantitative methods revealed the wide normal variation in laryngeal movements during the MI-E. This important information would have been missed in a qualitative design.

5.3.2. Statistics

Results in this study are based on the use of simple descriptive statistics, i.e.; counting of frequencies and percentages. These demonstrate an overview of laryngeal movements during MI-E and separate the prominent from the infrequent movements.

As with other forms of quantitative descriptive research, a sufficient number of subjects and observations per subject is needed for adequate internal and external validity (Thomas & Nelson, 1990: p.291). A formal power calculation is difficult to perform since there is no

previous information on which to base the estimates. The relatively small size of the sample complicates to some extent a generalization of the results, and larger samples could possibly have resulted in different conclusions. However, the aim of this study was not to firmly establish normal laryngeal physiology during MI-E, but to perform a pilot study that opens up for quantitative research an area that has not been explored.

Twenty healthy subjects examined in this presents study constitute the only study to date on normal laryngeal response pattern to MI-E.

5.3.3. TFL vs. other methods to visualize the laryngeal structures

A major challenge in this context is the lack of knowledge about this specific topic. An expected normal laryngeal response pattern to MI-E is unknown, as well as the required size of the laryngeal opening to allow free airflow during MI-E. The MI-E device aims to mechanically insufflate and exsufflate the lungs and to achieve this, an adequate sized laryngeal inlet is required (Pierce & Worsnop, 1999). The method of TFL does not explain the functional correlates of the observations. Enhancement of the PCF is the most important functional effect outcome for MI-E (Anderson, Hasney & Beaumont, 2005). This study does not show if the laryngeal movement pattern during MI-E affects PCF. Measurement of flow synchronized with the TFL examination is required to explore these functional issues. However, measurements in healthy individuals may not be relevant in the context of NMD, since healthy individuals manage to generate higher PCF values.

Sancho et al. (2004b) studied upper airways with CT scanning and visualized pharyngeal and oropharyngeal structures in three ALS patients. They did not examine the laryngeal level; nevertheless they generated a hypothesis that coordinated movements of the glottis are probably crucial for effectiveness of non-invasive use of MI-E. Their hypothesis was to a great extend based on a relationship between poor ability to generate PCF >160 l/min and bulbar dysfunction, suggesting poor laryngeal ability to generate a cough maneuver. An upward movement of the larynx during exsufflation may be an important point regarding the validity of the CT findings. A lifting of the larynx may cause obstruction of higher levels such as the oropharynx, where the greatest narrowing was observed.

CT scannings are costly and do not allow for simultaneous use of the MI-E device during the imaging procedure. TFL is much more flexible in terms of use during various interventions and use of technical aids, such as the MI-E. Nevertheless, both methods are mainly limited to hospital settings and depend on relatively advanced equipment and skilled healthcare personals.

The method of TFL allows for visualization of the hypopharynx, supraglottic and glottic structures, but not of the structures above the hypopharynx; an area which is better visualized with CT scanning. However, the visualized structures are displayed in detail and show their dynamic interactions during the complete cycle of MI-E, which will give a better functional understanding of these structures.

The study confirms that the examination with TFL visualizes the movements of the larynx; still the method has limitations. Although the technique of TFL is performed without sedation, with little discomfort and at no risk, it is an invasive maneuver that may irritate the upper airways and induce some discomfort. The latter may also influence the results due to the biopsychological aspects of discomfort, which may have an impact on laryngeal movements. Still, the subjects completed the complete examination and actually indicated afterwards that the examination was more gentle that they had excepted.

5.3.4. Observations of the laryngeal movements

An important factor in observational research is the operational definitions of the study; events and behaviors must be carefully defined to be observable (Thomas & Nelson, 1990: p.290). To assure that observations were performed from the continuous video recordings during this particular time frame of interest (the MI-E cycle) the video recordings of the MI-E device manometer was displayed on the same screen as the video of larynx.

A possible inadequate training in observation and evaluation can represent a major pitfall in this kind of study design. Effective observation requires practice. Evaluation of the video recordings was performed by me; a physiotherapist. Background as a physiotherapist has both advantages and limitations in observation of the laryngeal movements. Advantage is the experience from observations and analyzes of movements and functions in daily clinically work, since such observations and evaluations are an important part of clinical

physiotherapy. (Shumway-Cook & Woollacott, 2007: p.520). Limitation can be lack of experience to evaluate laryngeal structures. In recognition of this limitation, I went through an educational program with a senior laryngologist before performing the assessments. Also the video recorded examinations could be reviewed and played in slow motion, a technique that made interpretations easier. Generally technical aids, such as videotape are invaluable instruments in an observational design. It is of great advantage not having to write down observations at the time the events are occurring. Video recordings can be replayed as often as needed, which makes it possible to detect fine or rapid movements. (Thomas & Nelson, 1990: p.290 & 380; Polit & Beck, 2008: p.433). Also, classification and categorization, which is so important, can be done in a quiet environment after the subject has left, and in cooperation with skilled colleagues.

The observation scheme was prepared during the study and thereafter used in the evaluation. This became a tool, produced for this study. The observation scheme can be used further in examinations with this method, but their validity needs to be addressed.

5.3.5. Quality of the assessments of the laryngeal movements

An otolaryngologist controlled the results of the evaluation. The intention was to secure that the evaluation was reliable. The otolaryngologist had experience in evaluation of larynx, based on of assessing TFL video recordings of children, adolescents and adults with or without pathology. Generally observational research will benefit from having more than one observer (Thomas & Nelson, 1990: p.290) Assessment of inter-observer reproducibility of the findings from the present study may be of interest for the validation of the observation scheme.

When developing a new measurement method, the issue of measurement quality is of great concern (Domholdt, 2005: p.265). The reliability and validity of TFL during MI-E has not been examined, which is a weakness of this study. The reason for not performing formal reliability or validity assessments was mainly the time constraints imposed by the master study context. Measurement of reliability and validity of the evaluations would have strengthened the findings of this study and should be done in the future studies (Thomas & Nelson, 1990: p.343).

5.3.6. Intervention

Applied pressures during the intervention with MI-E

Clinically there is no simple algorithm or one method to adjust the MI-E settings suitable for all, and the literature varies widely regarding recommendations on this point (Chatwin, 2009; Homnick, 2007). The study used a wide range of pressure settings; ±20 to ±50 H_2O. This is the range of settings used also clinically, strengthening the clinical value of this study.

Airway pressure measurement during intervention with MI-E was performed with the intention to measure the accuracy of the pressure settings on the device. For technical reasons these measurements were completed in nine (of totally twenty) subjects. A lower mean airway pressure was measured at the mouth near the facemask than was set on the device. This is in agreement to the results of Faurox et al. (2008) who highlighted the inaccuracy between pressure settings on the device and the pressures measured in the facemask.

In our study the device accuracy was better during exsufflation than insufflation. A possible explanation may be a leakage of the mask during insufflation. Leakage may occur more easily during positive pressure than during negative pressure when the mask is sucked tight against the face. The results from airway pressure measurements confirm at least, that pressures higher than intended in the MI-E protocol were not applied.

The pressure during the intervention was increased gradually to familiarize the subjects to the feeling of MI-E. This can be a confounding factor; the subjects get familiarized with the feeling of mechanical insufflation-exsufflation through experience and modification of movements according to the theory of motor learning (Shumway-Cook & Woollacott, 2007: p.22). Randomizing the intervention sequences could prevent this, but in clinical settings pressures are always increased gradually in order to be as gentle as possible for patients and to get the individuals be familiar to the feeling of MI-E.

Instructions during intervention with MI-E

In my clinical practice, patients use the device also to prevent chest infections, not only to treat established pneumonia. In treatment with MI-E, patients are instructed to actively

inhale prior to the applied insufflation, even if the patients have poor ability to breathe in due to respiratory muscle weakness. The instructions indicates to the patient the upcoming insufflation (Chatwin, 2008). This will prepare the patient for the upcoming task and thereby facilitate that adequate movements are initiated (Shumway-Cook & Woollacott, 2007: p.5).

The study of Sancho et al. (2004b) intended to examine the pure effect of exsufflation. The aim of their study was to examine how PCF rates are generated by insufficient patient cooperation. The patients were not instructed to actively inhale or exhale since the authors argue that the patients are not able to do this due to their muscle weakness when suffering from pneumonia when they need MI-E, which they considered an important practical point.

As instructions influence motor response patterns, they may in fact become confounders; i.e. factors that may modulate outcome independent of the laryngeal response pattern. Still the instructions are an important factor in therapeutically treatment and thereby included as a natural part of the intervention.

5.3.7. Transferability of the method to further examination in patients

One aim of this study was to establish a foundation for further examination in patients. Clinical interventions with the aim to improve the motor control in patients with neurologic dysfunction should be based on an understanding of the nature of normal movements, as well as an understanding of the basis for abnormal movements (Shumway-Cook & Woollacott, 2007: p.8). Thereby, knowledge of the normal laryngeal response patterns to therapeutic intervention of MI-E is required prior to an evaluation in patients. It has been suggested by several authors that laryngeal function is important for successful use of the MI-E, but not until now we see what kind of importance this organ has. The present study has started to map out the laryngeal response patterns to MI-E; the first steps are taken with examinations of healthy subjects.

The present study has confirmed that in healthy subjects TFL during the use of MI-E may be considered safe and well-tolerated. This result indicates that the method of TFL may be useful in investigations also if the larynx is preventing effective use of MI-E in patients

with bulbar dysfunction. Whether or not the method works in patients with intrinsic laryngeal weakness is yet to be studied. One practical challenge may be that secretions can interrupt the video quality in patients who may have more airway secretions. If so, pre-treatment with MI-E can be considered in order to clear away secretions prior to the examination with TFL.

The study sample was very homogenous as regards baseline characteristics. Persons with ALS are a heterogeneous group, based on the progressive pathological picture of the disease and particularly the varying extent of bulbar function. The wide variation of responses to the MI-E observed in a homogeneous group of healthy persons indicates maybe also a wide variation in laryngeal movements in patients. The observation scheme that was prepared for this study can be used in evaluation of patients. Movements occurring in all healthy subjects, which are considered as voluntary movements, should be emphasized in observations also in patients. Possibly, this observation scheme should be modified if additional movements are observed in patients.

Since the laryngeal movements have not been evaluated earlier, there were no preexisting assessment scores that could be used directly in this study. Categorical data could not conclude on the issue of the grade of movements and patency of larynx. However, the present study generated a hypothesis that pressure settings may influence laryngeal and hypopharyngeal patency. Findings with both the narrowing of the vocal folds and the hypopharyngeal constriction during exsufflation indicate that these movements were more severe with high negative pressures, but statistically this was difficult to show.

To investigate this further, we need to establish a score system with a scale for movements also in patients. A score system based on findings in healthy people alone will most likely not be useful with patients as they are likely to response differently (Domholdt, 2005 p.261). A score system has been suggested, but requires evaluation also in patients. The establishment of a new method to evaluate a new phenomenon is a long-term process. Both the examinations and interpretation of the examinations should be validated and tested for reliability in relation to interrater -, intrarater - and intrasubject reliability in relevant patient populations. (Domholdt, 2005: p.257).

5.4. Clinical value of the study

MI-E was applied as in clinical practice; with pressure settings and instructions corresponding to what is used in patients. This may allow for information relevant to clinical practice. However, results obtained from healthy people are not directly applicable to a clinical setting, but may lead to theoretical modifications and may influence the clinicians to rethink clinical treatment measures. (Domholdt, 2005: p.18 & 48).

The opening of the laryngeal inlet is required to allow free air flow in and out of the airways. The phasic relationship between the PCA muscle and diaphragm is an important clinical practical point, also in treatment with MI-E. If there is a suspicion that the patient cannot "fill" the lungs with a positive pressure insufflation, the patients should be encouraged to breathe in prior to the applied insufflation. According to the motor control theory the task determines the required movement and constraints related to the tasks can impose constraints on the neural organization of the movement. However, in disease a consideration of underlying impairments is also needed, as abnormalities of reflex organization may explain disordered motor control in patients with neurologic disorders. (Shumway-Cook & Woollacott, 2007: p.5).

The individual approach physiotherapists use clinically both as regards pressure and time settings and instructions with the MI-E treatment is appropriate concerning laryngeal responses to MI-E. MI-E should not be thought of as a device that simply "fills up" and "empty" the lungs for air. High pressures may be required to obtain the flow rates that are necessary to obtain adequate PCF. High pressures also seem to turn on reflex mechanisms or initiate processes that lead to disadvantageous laryngeal anatomical alterations.

Anatomical variations considered to be within normal ranges may play a role for the laryngeal response patterns during MI-E. The quite frequently observed retroflex movement of the epiglottis during insufflation and the hypopharyngeal constriction during exsufflation indicate this. These movements may obstruct air flow and prevent increasing the PCF, which is an important goal for the treatment. These mechanisms may become even more important in patients with intrinsic laryngeal weakness.

Findings of this study may also be clinically beneficial for other patients (than ALS) with poor laryngeal coordination and inability to utilize MI-E, i.e. persons with multiple sclerosis and persons with extensive cognitive and functional disabilities. These patients

also have chest infections due to impaired ability to cough. Probably, the examination with TFL during MI-E can be used to evaluate these patients laryngeal response pattern.

In a clinical context when we are unsure if the limitation to success with MI-E is related to poor coordination or to anatomical characteristics in larynx, a TFL examination should be considered.

5.5. Future prospects

The extent to which pressures and instructions, or their combinations, influence movements is an important issue to investigate further. The way the data was categorized in this study did not seem to be sensitive enough to detect the variations of movements, and the classification scheme should therefore be refined. Application of the method in patients is necessary to develop a clinically useful score system. The method used in this study seems safe and may be considered to be used in persons with ALS to examine their laryngeal response pattern to MI-E.

ALS is progressive by nature, and the long term response pattern to MI-E in ALS seems important to investigate. Particularly, a gradual development of bulbar dysfunction may influence the extent to which a successful use of MI-E is to be expected. When we increase our understanding of these issues, we can hopefully develop better clinical instructions, more fine-tuned settings, or even new functions in the MI-E devices.

Enhancement of PCF is the most important effect outcome for MI-E. Therefore, measurement of airflow synchronized to the TFL during MI-E treatment would vastly increase our understanding of the functional correlates of the observations. Only through such measurements can we learn the functional consequences of what we observe, e.g. retroflex movement of the epiglottis or hypopharyngeal constriction.

Validity and reliability of the observations obtained with the TFL and of the evaluation of the observations should be examined in larger populations.

6. CONCLUSION

The larynx can be studied with transnasal laryngoscopy during MI-E in healthy individuals. Laryngeal movements during MI-E are influenced both by the instructions and the pressure settings that are applied. Healthy subjects manage to coordinate their glottic opening and closure according the task they are asked to perform, irrespective of the pressure settings on the MI-E. An initial abduction was observed during both insufflation and exsufflation. However, a variety of movements was observed subsequent to the initial abducting movements in all phases of the MI-E. One may speculate if the most common movements may be interpreted as voluntary, while movements occurring more infrequently may be understood as reflexes, released by the applied positive and negative pressures.

Findings from this study confirm that clinical respiratory physiotherapy should continue to have an individual approach to treatment with MI-E. Larynx is a complex structure and cannot simply be thought of as a passive valve through which one may insufflate and exsufflate the lungs with similar responses in all, particularly not in patients with intrinsic laryngeal weaknesses and reduced motor control.

These descriptions of laryngeal movements in healthy subjects may contribute to a better understanding of the heterogeneity of treatment responses to MI-E in patients with neuromuscular diseases. TFL may be an important examination to perform if the larynx is suspected to prevent effective use of MI-E. This may contribute to better clinical respiratory physiotherapy treatment of patients with bulbar muscle weakness.

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Forespørsel om deltakelse i forskningsprosjektet

Kartlegging og oppfølging av strupens funksjon hos personer med Amyotrofisk lateral sclerose (ALS)

Bakgrunn og hensikt med denne studien

Dette er et spørsmål til deg om å delta som frisk kontroll i en forskningsstudie som skal kartlegge hva som skjer i strupen hos pasienter med Amyotrofisk Lateral Sclerose (ALS) når de puster og hoster - og spesielt når de bruker en såkalt "hostemaskin". Vi tror at strupen kan være et viktig hinder for god hostefunksjon og derved et hinder for å få opp slim fra lungene hos disse pasientene. Dette er uheldig for pasienter med ALS og derfor viktig å undersøke nærmere.

Tolkning av resultater fra undersøkelser av pasienter med ALS må baseres på sammenligning med tilsvarende undersøkelse av friske personer (kontroller). Derfor vil vi også kontakte friske voksne med spørsmål om å delta i et tilsvarende undersøkelsesprogram. Resultatene fra undersøkelsene av kontrollene vil bli sammenlignet med resultatene fra de som har diagnosen ALS.

Ca 200-300 personer har ALS i Norge. Det er en sykdom som rammer hjernen og ryggmargen og som etterhvert leder til problemer bl.a. med å hoste og puste på grunn av svekkelse av muskulatur i bryst, tunge og hals. Behandling av ALS tar sikte på å opprettholde eller forbedre livskvaliteten lengst mulig.

Hostemaskin er et hjelpemiddel til å få opp slim fra luftveiene. Den virker ved at luft først forsiktig blåses inn i lungene og deretter suges ut sammen med slim fra de sentrale luftveiene. Vi opplever at flere ALS pasienter får god hjelp av hostemaskinen, mens den fungerer dårligere hos andre. Vi tror at hindringen kan ligge i strupen, men dette har ikke blitt undersøkt tidligere.

Målet med denne studien er å kartlegge strupens funksjon hos ALS pasienter over tid gjennom undersøkelser ved de regelmessige polikliniske kontrollene ved Haukeland Universitetssykehus (HUS). Bedre kunnskap på dette området kan bidra til bedre og mer individuelt tilpasset behandling hos pasienter med ALS. Dette vil kunne forbedre kvaliteten på behandlingen, også hos pasientene som deltar i denne aktuelle studien. Vi ønsker å lære av våre erfaringer slik at de kan bli til nytte også for andre pasienter. Derfor utføres undersøkelsene systematisk og innenfor rammene av en forskningsstudie. Forespørsel om deltagelse i denne studien er sendt til alle pasienter som er tilknyttet ALS klinikken på HUS.

Deltagelsen av friske kontroller innebærer

- Kartlegging av lungefunksjon.
- Inspeksjon av strupen med laryngoskopi mens hostemaskin blir testet ut med forskjellige innstillinger. Laryngoskopi betyr inspeksjon av strupen ved hjelp av en myk slange med kamera som føres forsiktig inn gjennom nesen slik at man kan kikke ned på stemmebåndene. Undersøkelsen utføres rutinemessig mange ganger daglig ved sykehuset. Kamera gjør videoopptak av strupen som kan studeres etterpå.

Undersøkelsene utføres poliklinisk på en time avtalt sammen med deg.

Mulige fordeler og ulemper
Alle undersøkelser er trygge. Inspeksjon av strupen kan medføre ubehag ved neseskilleveggen og en følelse av kiling i halsen. For å redusere ubehaget vil neseslimhinnen behandles med vanlig nesespray som brukes ved forkjølelse, og deretter lokalbedøves ved hjelp av en gel (Xylocain®). Undersøkelsen utføres av en lege som utfører denne type undersøkelser av både barn og voksne med spørsmål om sykdommer i øvre luftveier.

Hva skjer med informasjonen om deg?
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien, dvs til å øke forståelsen vår for hva som skjer i strupen hos pasienter med ALS når de puster og hoster og bruker hostemaskin. Alle opplysningene og resultatene fra undersøkelsene vil i en forskningssammenheng bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og resultater gjennom en navneliste. Det er kun personer knyttet til prosjektet som har adgang til denne navnelisten og som kan finne tilbake til deg. Alle som får innsyn i opplysninger har taushetsplikt. Det vil ikke være mulig å identifisere deg i resultatene fra studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dersom du ønsker å delta, undertegner du samtykke erklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Mer informasjon om studiet kan du få ved henvendelse til:
Tiina Andersen
Spesialfysioterapeut
Nasjonalt Kompetansesenter for hjemmerespiratorbehandling, HUS
Tlf. 55 97 84 86 / 80
Mob. 95 89 04 60
E-post tiina.andersen@helse-bergen.no

Det planlagte prosjektet er et samarbeidsprosjekt mellom [1]Nasjonalt kompetansesenter for hjemmerespiratorbehandling, [2]Lungeavdelingen, [3]Neurologisk avdelingen, [4]Øre Nese Hals avdeling, [5]Fysioterapiavdeling og [6]Barneklinikken på Haukeland Universitetssykehus, [7]Universitet i Bergen samt [8]Høgskolen i Bergen.

Ole-Bjørn Tysnes
Overlege, prof. dr med. [3, 7]

John-Helge Heimdal
Overlege, dr.med. [4]
Førsteamanuensis[7]

Thomas Halvorsen
Overlege, dr.med. [6]

Tiina Andersen
Spesialfysioterapeut [1, 2, 5, 8]

Ove Fondenes
Overlege, senterleder [1, 2]

Ola Drange Røksund
Spesialfysioterapeut [6, 8]

Samtykke til deltakelse i studien

Jeg er villig til å delta som <u>frisk kontroll</u> i studien

Kartlegging og oppfølging av stemmebåndets bevegelse og stabilitet hos personer med Amyotrofisk lateral sclerose (ALS)

Navn _____
(Bruk blokkbokstaver)

Sted og dato_____

_____
Underskrift av prosjektdeltaker

HOSTEMASKIN OG LARYNX – SCORINGSSKJEMA PÅ VIDEOOPPTAK

	Insuflasjon						Trykkfall						Eksuflasjon							Anatomisk
Intervensjon	Stemmebåndene åpnes	Stemmebåndene lukkes deretter	Aryepiglottiske foldene åpnes	Aryepiglottiske foldene lukkes	Epiglottis retroflex	Hypopharyngeal obstruksjon	Stemmebåndene åpen	Stemmebåndene lukket	Aryepiglottiske foldene åpen	Aryepiglottiske foldene lukket	Epiglottis retroflex	Hypopharyngeal obstruksjon	Stemmebåndene åpnes	Stemmebåndene forsnevres	Stemmebåndene lukkes (x-ganger)	Aryepiglottiske foldene åpnes	Aryepiglottiske foldene lukkes	Epiglottis retroflex	Hypopharyngeal obstruksjon	Beskriv
Pust																				
Forsert ekspirasjon																				
Hoste																				
1 20 I-E																				
2 20 I-C																				
3 20 I-sC																				
4 30 I-E																				
5 30 I-C																				
6 30 I-sC																				
7 40 I-E																				
8 40 I-C																				
9 40 I-sC																				
10 50 I-E																				
11 50 I-C																				
12 50 I-sC																				

Klarer Valsalva manører: ☐JA ☐NEI

APPENDIX 2 (1/1)

APPENDIX 3 (1/13)

Skjema: Prosjektgodkjenning

Sammendrag

1. Generelle opplysninger

a. Prosjekttittel

Prosjekttittel: Strupens funksjon ved amytrofisk lateral sclerose (ALS)
Vitenskapelig tittel: Laryngeal funksjon ved amytrofisk lateral sclerose (ALS)
Prosjektleder: THOMAS HALVORSEN
Forskningsansvarlig: Nasjonalt kompetansesenter for hjemmerespiratorbehandling
Initiativtaker: Prosjektleder eller forskningsansvarlig (Bidragsforskning)
Utdanningsprosjekt:
Studium: Mastergradsstudiet
Nivå: MSc
Norsk tittel Strupens funksjon ved amytrofisk lateral sclerose (ALS)
Vitenskapelig tittel Laryngeal funksjon ved amytrofisk lateral sclerose (ALS)

b. Prosjektleder

Navn	THOMAS HALVORSEN
Akademisk grad	DR MED
Klinisk kompetanse	PEDIATER
Stilling	OVERLEGE 50% og POSTDOKTOR UIB 50%
Hovedarbeidssted	HAUKELAND SYKEHUS OG UNIVERISITETET I BERGEN
Arbeidsadresse	BARNEKLINIKKEN
	HAUKELAND UNIVERSITETSSYKEHUS
Postnummer	5021
Sted	BERGEN
Telefon	55975200
Mobiltelefon	
E-post adresse	thomas.halvorsen@helse-bergen.no

c. Forskningsansvarlig

Forskningsansvarlig er	Institusjon eller annen juridisk person
Institusjon/juridisk person	Nasjonalt kompetansesenter for hjemmerespiratorbehandling
Gateadresse/postboks	Haukeland Universitetssykehus

Postnummer	5021
Sted	Bergen
Kontaktperson	Ove Fondenes
Stilling	Overlege / Senterleder
Telefon	55978482
Mobiltelefon	95890446
E-post adresse	ove.fondenes@helse-bergen.no

d. Prosjektplassering

Initiativtaker til prosjektet	Prosjektleder eller forskningsansvarlig (Bidragsforskning)
Utdanningsprosjekt/doktorgradsprosjekt	Ja
Studium	Mastergradsstudiet
Nivå	MSc

e. Prosjektmedarbeidere

Prosjektmedarbeider 1	Ja
Navn	Ove Fondenes
Stilling	Overlege / Senterleder
Institusjon	Nasjonalt kompetansesenter for hjemmerespiratorbehandling
Akademisk grad	MD
Prosjektrolle	Veileder
Prosjektmedarbeider 2	Ja
Navn	Tiina Andersen
Stilling	Spesialfysioterapeut
Institusjon	Nasjonalt kompetansesenter for hjemmerespiratorbehandling
Akademisk grad	MSc student
Prosjektrolle	Daglig leder
Prosjektmedarbeider 3	Ja
Navn	Ole-Bjørn Tysnes
Stilling	Avdelingssjef, overlege
Institusjon	Neurologisk avdeling, HUS

Akademisk grad	Prof. dr. med.
Prosjektrolle	Veileder
Prosjektmedarbeider 4	Ja
Navn	Ole Røksund
Stilling	Spesialfysioterapeut
Institusjon	Barneklinikken, HUS
Akademisk grad	PhD student
Prosjektrolle	Veileder
Prosjektmedarbeider 5	Ja
Navn	John-Helge Heimdal
Stilling	Klinikksjef
Institusjon	Øre Nese Hals avdeling, HUS
Akademisk grad	PhD
Prosjektrolle	Veileder

2. Prosjektopplysninger

a. Bakgrunn og formål

Prosjektleders prosjektomtale	Amyotrofisk lateral sclerose (ALS) er en sykdom i hjernen og ryggmargen som bl.a. påvirker respirasjonen og evnen til å hoste pga muskelsvekkelse i bryst, tunge og hals. Behandlingen er symptomatisk, med hensikt å opprettholde livskvaliteten lengst mulig. Hostemaskin er et hjelpemiddel for å få opp slim fra luftveiene hos disse pasientene. Hostemaskinen fyller først lungene med luft og deretter suges luften og slimet ut fra de sentrale luftveiene. Vi opplever at flere ALS pasienter får god hjelp av hostemaskinen. Imidlertid er det enkelte som ikke ser ut til å bli hjulpet. Vi tror at årsaken til dette ligger i strupen, men dette har ikke blitt undersøkt tidligere. Målet med studiet er å kartlegge funksjon i strupen hos personer med ALS, samt følge dette opp over tid. Bedre kunnskap om strupens funksjon kan bidra til bedre og mer individuelt skreddersydd behandling i forhold til pusteproblemer og slimmobilisering.

b. Forskningsdata

Nye helseopplysninger	Ja
Spesifiser hvilke typer helseopplysninger	Opplysninger om høyde, vekt og kjønn. Opplysninger om diagnose, sykdomsdebut og symptomer, evt. hjemmerespiratorbehandling og tidligere bruk av hostemaskinen. Opplysninger om helserelatert livskvalitet. Klinisk nevrologisk undersøkelse. Kartlegging av lungefunksjon. Undersøkelsen med transnasal fiberoptisk laryngoskopi med video opptak av larynx mens man puster, hoster, svelger, uttaler bestemte ord og hoster med hostemaskinen med forskjellige innstillinger. Opplysninger om personens opplevelse om å få luft inn / ut ved bruk av hostemaskinen. Flow, volume og trykk målinger fra utprøving av hostemaskinen.

c. Forskningsmetode

Prosjektet er	Kvantitativt
Klinisk undersøkelse	Ja
Spørreskjema	Ja
Observasjon	Ja
Film/video	Ja
Faglig og vitenskapelig begrunnelse for valg av metode	Hensikten med studien er å utvikle ny kunnskap om strupens funksjon og hvordan denne utvikler seg hos ALS pasienter under progresjon av sykdommen. Vår hypotese er at transnasal fiberoptisk laryngoskopi med video opptak av larynx mens pasienten puster, hoster, svelger og bruker hostemaskin, kan gi viktig kunnskap om ALS pasientenes laryngeale funksjon og derved bidra til en bedre forståelse av respons - eventuelt manglende respons - på sekretmobiliserende behandling. Selve undersøkelsen er kortvarig, men videoopptak tillater grundig vurderingen blant annet i sakte film av visualiserte mekaniske forhold, stabilitet og bevegelser i larynx. Opptakene vil vurderes av erfarne fagpersoner (øre-nese-hals lege og logoped). Transnasal fiberoptisk laryngoscopi av strupen er en etablert undersøkelse og en gullstandard når det gjelder diagnostikk av stemmebånds-dysfunksjon. Den har også blitt brukt hos ALS pasienter for å evaluere stemmebåndenes funksjon. Sammen med den visuelle fremstillingen av larynx vil måling av flow, volum og trykkforhold i munn og slanger fra hostemaskinen, gi oss et bilde av pasientens respons på behandlingen. Målinger kan også bidra med verdifull kunnskap om hvorvidt bestemte innstillinger er av betydning

for stabilitet i larynx eller om endringer av slike innstillinger kan påvirke flow under hoste, som er effektmålet for hostemaskinen. Klinisk er det i dag ikke mulig å forutse hvilke pasienter som vil ha effekt av hostemaskinen. Studiens ambisjon er å finne fram til gode prediktive undersøkelser som kan hjelpe oss til å optimalisere den slimmobiliserende behandlingen ved ALS. Laryngoskopisk undersøkelse har ikke tidligere blitt brukt sammen med hostemaskin. Derfor ønsker vi å undersøke at hvordan dette tolereres. Vi ønsker derfor å gjennomføre en pilot-studie med friske personer i forkant av testing av ALS pasienter. Dersom metoden fungerer bra og tolereres godt, vil ALS pasienter bli undersøkt i en tverrsnittstudie. De første ALS pasientene vi undersøker, vil være nydiagnostiserte og ha liten påvirket pustekraft. Tverrsnittstudien vil undersøke ALS pasientenes laryngeale funksjon og stabilitet ved spontan pust, hoste, svelging og uttalelse av enkelte ord. I tillegg vil hostemaskinen bli brukt som en klinisk intervensjon med standardisert protokoll med forskjellige innstillinger. Tverrsnittstudien samler informasjon på planlagt måte i definert utvalg på et gitt tidspunkt. ALS er en progressiv og 100 % dødelig sykdom. Vi ønsker å undersøke hvilken rolle laryngeal funksjon spiller i denne progresjonen. Vi ønsker dessuten å undersøke i hvilken grad en eventuell økende laryngeal dysfunksjon påvirker effekt av behandling og livskvalitet. Tverrsnittstudien vil derfor bli fulgt opp med tilbud om deltagelse i en longitudinell studie. Undersøkelsene fra tverrsnittsstudien vil bli gjentatt ved de vanlige polikliniske kontroller på ALS klinikken ca hver tredje måned. Pasientene vil bli undersøkt med kortvarige laryngoscopier under vanlig pusting, svelging og spontan hoste. Vi vil dessuten evaluere et eventuelt tap av effekt fra behandling med hostemaskin ved hjelp av laryngoskopi. Vi vil bruke hostemaskinen på samme måte i denne studien som vi ville ha gjort uten denne studien, det vil si at bruken vil bli redusert og eventuelt stanset når toleransen for behandlingsmetoden ser ut til å avta klinisk. Det eneste tilleggsmomentet studien påfører pasienten, er at det gjøres en kortvarig laryngoskopi under gjennomgangen av behandlingen slik dette alltid blir gjort ved de rutinemessige polikliniske kontrollene. Dersom vi ved laryngoskopien gjør funn som støtter en klinisk mistanke om at behandlingen begynner å miste sin effekt, kan dette få direkte positiv effekt for pasienten ved at en unyttig behandling kan stanses.

d. Utvalg

Pasienter/klienter	Ja
Spesifiser hvilke pasienter	Tverrsnittsundersøkelsen vil inkludere alle pasienter med diagnosen ALS som ikke er trakeostomert, og som blir fulgt opp av ALS klinikken ved Haukeland Universitetssykehus. Deltagere fra tverrsnittsstudien ønskes også å følges opp i den longitudinelle studien. Eksklusjonskriterier er alder under 18 år, sykehistorie med laryngospasmer, trakeostomi, pneumothorax, barotrauma, lungesykdom eller kreft, samt mentalt ustabile pasienter.
Begrunn valg av pasientgruppe	Behandling av ALS tar sikte på å opprettholde eller forbedre livskvaliteten lengst mulig. Når sykdommen utvikler seg, får ALS pasienter ofte problemer med slim i luftveiene som de ikke klarer å hoste opp med egen hjelp. Så kalt hostemaskin, som bruker teknikken mekanisk insuflasjon-eksuflasjon, har vist å være det mest effektive tiltaket for å forbedre hoste-evnen hos pasienter med neuromuskulære sykdommer og skader. Per dags dato prøver vi ut hostemaskinen hos alle ALS pasienter med slimproblemer. Vi opplever at flere ALS pasienter får god hjelp av hostemaskinen, mens den fungerer dårligere hos andre. Det er foreslått at de nevromuskulære strukturene i strupen hos noen ALS pasienter ikke fungerer godt nok sammen med hostemaskinen. Dette har imidlertid aldri vært studert skikkelig. Vi tror at strupen kan være et viktig hinder for god hostefunksjon og derved et hinder for å få opp slim fra lungene. Dette er uheldig for pasienter med ALS og derfor viktig å undersøke nærmere. Bedre kunnskap på dette området kan bidra til bedre og mer individuelt tilpasset behandling hos pasienter med ALS. Dette vil kunne forbedre kvaliteten på behandlingen, også hos pasientene som deltar i denne aktuelle studien.
Kontrollgruppe(r)	Ja
Spesifiser hvem som skal inngå i kontrollgruppen (e)	Friske voksne studenter (både medisin- og fysioterapistudenter).
Begrunn valg av kontrollgruppe(r)	Tolkning av resultater fra undersøkelser av ALS pasienter må baseres på sammenligning med tilsvarende undersøkelse av friske personer (kontroller). Derfor vil vi kontakte friske voksne, som vil få forespørsel om å gjennomføre de samme laryngoskopi-undersøkelsene som planlegges hos ALS pasientene. De friske vil bli undersøkt før ALS pasientene blir kontaktet.

	Dette sørger for at metoden med laryngoskopi sammen med hostemaskin blir testet å være trygg og veltolerert. Resultatene fra undersøkelsen av kontroller vil beskrive hva som skjer i larynx hos friske når man bruker hostemaskinen.

e. Omfang

Norge	20 friske kontroller og ca. 20 ALS pasienter
Redegjør og begrunn prosjektets omfang	Vi ønsker å inkludere så mange ALS pasienter som mulig når studiet pågår, slik at vi kan publisere populasjonsbaserte data. Det er vanskelig å beregne endelig antall pasienter som blir inkludert siden ALS er en sykdom som progredierer relativt raskt i tillegg til at det ikke finnes helbredende behandling og pasientene kan dø allerede 1-3 år etter diagnostisering. Per dags dato følger ALS klinikken ved HUS opp 14 ALS pasienter uten trakeostomi, men nye pasienter diagnostiseres med jevne mellomrom, circa 8 stk per år. Vi har valgt 20 friske kontrollpasienter ettersom dette antas å gi en ca 1:1 ratio i forhold til pasientpopulasjonen.
Styrkeberegning	En formell styrkeberegning blir vanskelig å gjøre for denne studien. Studien er først og fremst en populasjonsbasert klinisk observasjonsstudie av den pasientpopulasjonen som til enhver tid følges opp ved ALS klinikken ved HUS og som tilfredsstiller inklusjonskriteriene. Studien vil levere deskriptive data fra et gitt tidspunkt samt longitudinelle oppfølgingsdata for de samme pasientene. Studien planlegger ingen intervensjon eller gruppesammenligning. Dessuten finnes det ikke data for spredningen av de utfallsmålene som skal følges. Data for spredning er en forutsetning for matematiske styrkeberegninger. Et mulig scenario er at resultater fra studien kan bli publisert som en serie med longitudinelle kasuistikker som evt kan fungere hypotesegenererende.

2C. Biobank

3. Samtykke og personvern

a.

b.

Samtykke innhentes	Ja
For hvilke data skal samtykke innhentes?	Alle
Spesifikt informert aktivt skriftlig samtykke	Ja
Redegjør for tiltak for å sikre et informert og fritt samtykke og begrunn eventuelle avvik fra anbefalte prosedyrer	Aktuelle deltagerer vil motta muntlig informasjon om studiet i tillegg til skriftlig informasjonsskriv og erklæring om samtykke. Det opplyses at å være med i studien er frivillig og krever skriftlig informert samtykke. Alle aktuelle deltagere får betenkningstid slik at de kan rådføre seg med andre ved behov. Prosjektdeltageren må undertegne en samtykkeerklæring før deltagelse på prosjektet. Deltagerne kan trekke seg fra studien uten at det medfører noen plikt for begrunnelse på et hvilket som helst tidspunkt. Dersom man velger å ikke delta, trenger man ikke oppgi grunn for dette. Det vil ikke påvirke pasientens behandling ved sykehuset om man deltar eller ei.

c.

4. Etisk vurdering av fordeler og ulemper

a. Fordeler

Den enkelte prosjektdeltaker	Ja
Angi hvilke fordeler	Hver enkelte ALS pasient vil få grundig evaluering av om hostemaskinen er et aktuelt hjelpemiddel. Nøye og regelmessige undersøkelser av den laryngeale funksjonen vil forbedre kvaliteten på behandlingen, også hos pasientene som deltar i denne aktuelle studien.
Grupper av personer	Ja
Angi hvilke grupper	Pasienter med ALS og andre pasienter med tilsvarende bulbær dysfunksjon.
Angi hvilke fordeler	Hos pasienter med ALS og hos andre pasienter med tilsvarende bulbær dysfunksjon, kan strupen være et viktig hinder for effektiv hoste og derved et hinder for å få opp slim fra lungene. Dette er uheldig, og derfor viktig å undersøke nærmere. Ny kunnskap om potensiell nytte av hostemaskin hos ulike fenotyper av ALS, kan gi økt kvalitet i behandling av slimplager, noe som er grunnleggende viktig for å forebygge og behandle lungebetennelser. Lungebetennelse er den viktigste dødsårsaken hos disse pasientene. Kunnskapen vil komme til nytte også for andre pasienter med tilsvarende problemer med bulbær

	dysfunksjon og redusert evne til hoste. Pasienter henvises vanligvis til opplæring og utprøving av hostemaskin relativt sent i forløpet. Gjennom deltagelse i dette prosjektet vil de få dette tilbudet på et langt tidligere stadium med de muligheter for helsegevinst som dette innebærer. Trakeostomi hos pasienter med ALS er en meget sammensatt klinisk og etisk problemstilling. Etter nøye vurderinger vil noen ALS pasienter være aktuelle for trakeostomi. Det finnes ikke klare anbefalinger for hvilket tidspunkt som er det optimale for å utføre dette. En bedre forståelse av hvilken rolle økende laryngeal dysfunksjon spiller ved progresjon av ALS vil kunne bidra til dette.
Vitenskapen	Ja
Angi hvilke fordeler	Det finnes ennå ikke kunnskap om hva skjer i larynx når man bruker hostemaskin. Den bulbære funksjonen ansees som viktig for at pasienter kan få nytte av dette mekaniske hjelpemiddelet. Beskrivelse av det laryngeale bevgelsesmønsteret og stabilitet ved bruk av hostemaskin med standardisert protokoll (forskjellige trykk og ulike kliniske instruksjoner og bruk av manuell hostestøtte i tillegg) kan øke vår forståelse om optimal klinisk bruk av dette hjelpemiddelet.

b. Ulemper

Den enkelte prosjektdeltaker	Ja
Angi hvilke ulemper	Den første undersøkelsen med hostemaskin og laryngoskopi gjøres utenom de vanlige polikliniske kontrollene som ALS pasienter uansett kommer til ved ALS klinikken ved Nevrologisk Avdeling og ved Lungeavdelingen, HUS. Senere gjøres alle undersøkelser i forbindelse med avtalte regelmessige polikliniske kontroller ca hver 3 måned. Studiedeltagelsen innebærer følgelig at pasientene må komme ekstra til sykehuset kun for en undersøkelse. Introduksjon av laryngoskop gjennom nesen og inspeksjon av strupen kan medføre ubehag ved neseskilleveggen og en følelse av kiling i halsen. Pasientene skal kun gjennomføre ordinære og dagligdagse øvelser med skopet på plass, det vil si bruke stemmen, puste, hoste og svelge. I tillegg skal de prøve ut hostemaskinen slik de forøvrig ville ha gjort dette - uavhengig av denne studien. Forskjellen er kun at de nå vil prøve dette ut med laryngoskopet i nesen.

c. Tiltak

Redegjør for særlige tiltak for å ivareta og beskytte deltakere i forskningsprosjektet	Laryngoskopisk undersøkelse av strupen er en godt etablert klinisk metode og gullstandard ved diagnostikk av stemmebånds dysfunksjon. Metoden har også blitt brukt hos ALS pasienter. Så vidt vi vet, har laryngoskopi ikke blitt brukt til å beskrive laryngeal funksjon ved bruk av hostemaskinen. Vi vil derfor teste dette hos friske kontrollpersoner. Dette vil bli gjort i en pilotstudie før pasientene blir kontaktet. Alle undersøkelser foregår på sykehuset, det vil si det er akuttmedisinsk kompetanse i den umiddelbare nærhet om det skulle oppstå uventede komplikasjoner eller bivirkninger. Lege er fysisk til stede under hele undersøkelsesprogrammet. For å redusere ubehaget ved innføring av laryngoskopet, vil neseslimhinnen bli behandlet med vanlig avsvellende nesespray som brukes ved forkjølelser, og deretter lokalbedøves ved hjelp av en gel (Xylocain®). Laryngoskopisk undersøkelse av ALS pasienter vil utføres av en erfaren øre-nese-hals lege som utfører denne type undersøkelser daglig av både barn og voksne med spørsmål om sykdommer i øvre luftveier. Dersom det er kjent sykehistorie med larygospasmer, vil pasientene bli ekskludert fra studien.

d. Forsvarlighet

Redegjør for din avveining mellom fordeler og ulemper og gi din begrunnelse for hvorfor du mener det er forsvarlig å gjennomføre prosjektet	Pasienter med ALS er mye plaget av slim og etter hvert tap av evne til å hoste, spesielt i sen fase av sykdommen. Dette representerer risiko for lungebetennelser og dermed risiko for tidlig død. Opphopning av slim uten mulighet for å kunne hoste er en svær psykisk belastning og en viktig årsak til tap av livskvalitet hos disse pasientene. Bruk av hostemaskinen er etablert behandling, men kunnskap om hvilke pasienter som har best utbytte av behandlingen mangler. Pasienter henvises vanligvis til opplæring og utprøving av hostemaskin relativt sent i forløpet. Gjennom deltagelse i dette prosjektet vil de få dette tilbudet på et langt tidligere stadium med de muligheter for helsegevinst som dette innebærer. Deltagelsen innebærer bruk av vanlige og forsvarlige undersøkelser med liten risiko og forholdsvis lite plager. Vi er av den oppfatning av at potensielle risikomomenter og ubehag er små og at gevinstpotensialet er stort.

5. Sikkerhet, interesser og publisering

a. Personidentifiserbare opplysninger

Opplysninger som registreres i prosjektet er direkte personidentifserbare	Ja
Navn, adresse og eller fødselsdato	Ja

b. Internkontroll og sikkerhet

PC tilhørende virksomheten og i nettverkssystem tilknyttet Internett	Ja
Videopptak/fotografi	Ja
På PC	Ja
Lydopptak	Ja
På PC	Ja
Annen oppbevaringsmåte	Ja
Redegjør for annen oppbevaringsmåte	Video opptakene av undersøkelsen med laryngoskopi vil være på CD plater. CD platene er merket kun med referansenummer uten direkte personidentifiserbarte opplysninger. CD platene vil oppbevares i låst skap på låst rom i sykehuset.
Koblingsnøkkel og opplysninger oppbevares atskilt fra hverandre	Ja
Passordbeskyttet oppbevaring	Ja
Innelåst oppbevaring	Ja
Redegjør nærmere for hvordan personidentifiserbare opplysninger er beskyttet mot innsyn fra uvedkommende	Direkte personidentifiserbare opplysninger (navn, addresse og fødselsdato) erstattes med et referansenummer som viser til en elektronisk navneliste som oppbevares atskilt fra det øvrige datamaterialet på dertil egnet sted for kodenøkler på HUS sin forskningsserver.

c. Forsikringsdekning for deltakere

Pasientskadeerstatningsloven	Ja

d. Vurdering av andre instanser

Egen institusjon	Ja

e. Interesser

Finansieringskilder	Haukeland Universitets sykehus, Nasjonalt kompetansesenter for hjemmerespiratorbehandling.

Godtgjøring til institusjon	Ingen
Honorar prosjektleder/-medarbeidere	Ingen
Kompensasjon for forskningsdeltakere	Ingen
Eventuelle interessekonflikter for prosjektleder/-medarbeidere	Ingen

f. Publisering

Redegjør for hvordan resultatene skal gjøres offentlig tilgjengelig	Offentliggjøring av masteroppgave (Master i Klinisk Fysioterapi) Presentasjon av vitenskapelig abstract på internasjonal medisinsk kongress. Publisering av artikler i internasjonalt vitenskapelig tidskrift. Foredrag i relevante lokale, nasjonale og internasjonale fora.

g. Offentlig innsyn

h. Tidsramme

Prosjektstart dato	02.05.2011
Prosjektslutt dato	01.06.2016
Etter prosjektslutt skal datamaterialet avidentifiseres	Ja
Redegjør nærmere for håndtering av data etter prosjektslutt	ALS er en 100% dødelig sykdom hvor de fleste dør 1-3 år etter diagnosen. Vi pålanlegger en longitudienell studie hvor pasienter skal følges fra diagnose til død. Vi må derfor ha datamateriale tilgjengelig minimum i 3-5 år etter inklusjonsperiode. Deretter kan datamaterialet avidentifiseres.

6. Vedlegg

1. SF-36.pdf - Spørreskjema om livskvalitet - 21.03.11
2. Stemme evaluering.pdf - Spørreskjema - 21.03.11
3. Spørreskjema.pdf - Spørreskjema - 21.03.11
4. Informert samtykke for friske deltagere.pdf - Forespørsel om deltagelsen til friske - 21.03.11
5. Informert samtykke for ALS pasienter.pdf - Forespørsel om deltakelse - 21.03.11
6. Study protocoll Laryngeal stability in ALS.docx - Forskningsprotokoll - 21.03.11

7. Ansvarserklæring

a.

Jeg erklærer at prosjektet vil bli gjennomført i henhold til gjeldende lover, forskrifter og	Ja

retningslinjer

Jeg erklærer at prosjektet vil bli gjennomført i samsvar med opplysninger gitt i denne søknaden	Ja
Jeg erklærer at prosjektet vil bli gjennomført i samsvar med eventuelle vilkår for godkjenning gitt av REK eller andre instanser	Ja

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Anne Berit Kolmannskog	55978496	06.05.2011	2011/784/REK vest
			Deres dato:	Deres referanse:
			22.03.2011	

Vår referanse må oppgis ved alle henvendelser

Thomas Halvorsen
thomas.halvorsen@helse-bergen.no
Nasjonalt kompetansesenter for hjemmerespiratorbehandling

Strupens funksjon ved amytrofisk lateral sclerose (ALS) 2011/784

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional forskningsetisk komité for medisinsk og helsefaglig forskningsetikk,Vest-Norge (REK Vest) i møtet 14.04.2011.

Prosjektomtale (revidert av REK):
REK Vest anser Helse Bergen HF som forskningsansvarlig for prosjektet. Formålet med denne studien er å kartlegge strupens funksjoner over tid hos pasienter med amyotrofisk lateral sclerose (ALS). Sykdommen gir muskelsvekkelser i bryst, tunge og hals og reduserer evnen til å hoste. Noen pasienter oppnår ikke lindring av hostemaskin som hjelpemiddel og en ønsker å undersøke om dette kan relateres til strupefunksjonen. 20 friske kontroller og rundt 20 ALS-pasienter ønskes inkludert i studien.

Forskningsetisk vurdering
Komiteen mener dette er en godt gjennomarbeidet studie med relevant problemstilling.
En har ingen innvendinger til forelagt protokoll.

Dataoppbevaring
I henhold til søknad skal forskningsprosjektets data oppbevares forsvarlig.
Prosjektslutt er satt til 01.06.2016. Personidentifiserbare forskningsdata skal anonymiseres eller slettes straks det ikke lenger er behov for dem og senest fem år etter prosjektslutt.

Prosjektet skal sende sluttmelding til REK vest på fastsatt skjema senest 01.12.2016.

Vedtak
Prosjektet godkjennes i samsvar med forelagt søknad.

Med vennlig hilsen,

Jon Lekven (sign.)
leder

Anne Berit Kolmannskog
sekretariatsleder

Kopi til: ove.fondenes@helse-bergen.no,
postmottak@helse-bergen.no

Saksbehandlingen følger forvaltningsloven. Komiteenes vedtak etter forskningsetikklovens § 4 kan påklages (jfr. forvaltningsloven § 28) til Den nasjonale forskningsetiske komité for medisin og helsefag. Klagen skal sendes REK Vest (jfr. forvaltningsloven § 32). Klagefristen er tre uker fra den dagen du mottar dette brevet (jfr. forvaltningsloven § 29).

De regionale komiteene for medisinsk og helsefaglig forskningsetikk foretar sin forskningsetiske vurdering med hjemmel i helseforskningsloven § 10, jfr. forskningsetikkloven § 4. REK Vest forutsetter at dette vedtaket blir forelagt den forskningsansvarlige til orientering. Se helseforskningsloven § 6, jfr. § 4 bokstav e.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no. Vennligst oppgi vårt referansenummer i korrespondansen.