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Kanditatnummer: 1

A feasibility study of how the expiration time impact the efficacy of MI-E in healthy adults.

A quantitative study

Master of thesis in Interdisciplinary health science

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Abstract

Introduction: Mechanical insufflation-exsufflation (MI-E) is a technique used to augment cough in individuals with neuromuscular disorders (NMDs). How variation in exsufflation time (T_e) influence efficacy has not been systematically assessed.

Aims: Before launching a study in patients, we aimed to examine study feasibility (protocol, instruments and outcome measures) in healthy adults, and to determine several measures of MI-E efficacy and their possible correlations, at a wide range of T_e settings.

Design: A feasibility study with an explorative cross-sectional design.

Methods: Airflow- and pressure curves were registered in healthy volunteers with a flow and pressure gauge (Citrex H5) while performing MI-E according to a standardized protocol applying pressures of ±40 cmH_2O for six MI-E cycles. The double-blinded procedure tested T_e of 0.5/1.0/1.5/2.0/2.5/3.0/3.5/4.0 second in a randomized order. A total of 960 cough cycles were analyzed for Peak Cough Flow (PCF), Effective Cough Time (ECT) and Effective Cough Volume (ECV). Correlations were assessed by Spearman Rank Order Correlation (rho).

Main results: Twenty healthy volunteers (65% women) completed the test protocol. The questionnaire of self-perceived effect and comfort failed to capture the VAS scores of every cough cycle and protocol shows therefore not to be feasible. The pneumotachograph had a limit of 300 l/min and is not feasible in healthy persons.

There was no correlation between T_e and PCF (rho .039, p>.001). There was a small positive correlation between T_e and ECV (rho .247, p<.001), a medium positive correlation between T_e and ECT (rho .326, p<.001), and between PCF and ECT (rho .326, p<.001) There was a strong positive correlation between PCF and ECV (rho .768, p<.001) and between ECV and ECT (rho .751, p<.001).

Conclusion: Protocol and pneumotachograph were not feasible in healthy volunteers. The pneumotachograph (Citrix H5) is not a feasible instrument for flow registrations in healthy individuals. Questionnaire of self – perceived effect and comfort is not feasible in healthy adults and needs to be rectified for a future study. ECT and ECV are more sensitive to T_e than PCF and are feasible outcome measures in the assessment of the efficacy of MI-E. Individualization of T_e may be an important factor to improve the efficacy of MI-E.

Sammendrag

Introduksjon: Hostemaskin med teknikken mekanisk innsufflasjon – eksufflasjon (MI-E) er en teknikk som benyttes for å gi støtte ved inn- og utpust i hostefasen og mobilisere slim hos personer med nevromuskulære sykdommer (NMS). Det er ikke tidligere undersøkt hva utpusttiden ($T_{e)}$ har å si for effekten av MI-E.

Hensikt: Før hovedstudien med pasienter ønsket vi å undersøke gjennomførbarheten av studiedesignet (protokoll, instrument og utfallsparametere) med friske frivillige. Vi ønsket også å sammenlikne nye utfallsparametere for effekt med det etablerte samt at vi ønsket å se på mulige sammenhenger mellom de og utpusttidene (T_e).

Design: En kvantitativ studie og en feasibility studie med et eksplorativt tverrsnittsdesign.

Metode: Under den standariserte testprosedyren ved MI-E, med ±40 cmH_2O, ble alle luftstrøms- og trykk-kurver registrert av en flow og trykk-måler (Citrex H5). Alle deltakere gjennomgikk seks hostesykluser for hver tidsinnstilling. T_e 0.5/1.0/1.5/2.0/2.5/3.0/3.5/4.0 kom i randomisert rekkefølge og prosedyren var dobbelt blindet. Totalt 960 host ble analysert. Sammenhenger mellom T_e, Peak Cough Flow (PCF), Effektiv hostetid (ECT) og Effektivt hostevolum (ECV) ble undersøkt ved hjelp Spearman Rank Order Correlation (rho) korrelasjonsanalyse.

Resultater: Tyve friske frivillige (65% kvinner) fullførte testprotokollen. Studien er gjennomførbar med friske voksne, men protokollen for selvrapportert effekt og komfort klarte ikke fange opp VAS skårene på alle hostesyklusene og kan derfor ikke benyttes. Flowmåleren hadde en maksverdi på 300 l /min og kan ikke benyttes ved testing av friske personer. Det var ingen sammenheng mellom T_e og PCF (rho .039, p>.001). Det var en svak positiv sammenheng mellom T_e og ECV (rho .247, p<.001), medium positiv sammenheng mellom T_e and ECT (rho .326, p<.001) samt mellom PCF og ECT (rho .326, p<.001). Det var en sterk positiv sammenheng mellom PCF og ECV (rho .768, p<.001) samt mellom ECV og ECT (rho .751, p<.001).

Konklusjon: Grunnet utformingsfeil av protokoll for selvrapportet effekt og komfort er ikke protokoll gjennomførbar med friske frivillige. Flowmåleren (Citrix H5) kan ikke benyttes til flowregistreringer av friske voksne. Utfallsparameterene PCF, ECT og ECV kan benyttes til å evaluere effekten av hostemaskin. ECT og ECV er mer sensitive for T_e enn det PCF er kan bidra til en mer nyansert vurdering av effekt ved MI-E. Tilpasset T_e kan være en viktig faktor for bedring av effekt ved MI-E.

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I would like to express my humble gratitude to my family, my husband and two children, for facilitating this and making it at all possible to study in combine with work and being a mum and wife. A special thanks to my two children for their patients and understanding all the times mum had to study instead of reading you bedtime stories and for all the times I had to stay home to study instead of skiing or hiking with you. I´m proud of you and I love you to the moon and back!

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Thanks to the leader of Norwegian Registry for Long-Term Mechanical Ventilation (LTMV) Solfrid Indrekvam, for granting us access to data for the future study (LTMV is in collaboration with the Norwegian Centre of Excellence in Home Mechanical Ventilation, Department of Thoracic Medicine, Haukeland University Hospital, Bergen. The register is funded by the Western Norway Regional Health Authority).

I am happy to say that this project is a collaboration between National Centre of Competance for Long – Term Mechanical Ventilation at Haukeland University Hospital, National Registry for Long-Term Mechanical Ventilation – LTMV at Haukeland University Hospital and Unit for Congenital and Hereditary neuromuscular disorders (EMAN) at Oslo University Hospital.

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NMD Neuromuscular disorder

MI-E Mechanical insufflation – exsufflation

PCF Peak Cough Flow

ECT Effective Cough Time

ECV Effective Cough Volume

VAS Visual Analog Scale

VC Vital Capacity

FVC Forced vital capacity

FEV1 Forced expiratory volume first second

MIP Maximum Inspiratory Pressure

MEP Maximum Expiratory Pressure

n Sample size

T_e Exsufflation time

MDT Multi-diciplinary team including neuro – physical therapist

NIV Non – invasive ventilation

SOB Shortness of breath

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1. Introduction

Neuromuscular disorders (NMD) may lead to muscle weakness which may involve the respiratory muscles (Hutchinson & Whyte, 2008).

When respiratory muscles are affected, the respiratory function and the cough efficiency may be impaired, and mechanical ventilation and mechanical cough assistance, using mechanical insufflation-exsufflation (MI-E), may be indicated (Bach, Ishikawa & Kim, 1997), (Chatwin et al., 2003).

The mechanical ventilation aims to compensate the failing respiratory function and the MI-E aims to assist airway clearance to prevent and treat pulmonary infections (Chatwin et al., 2003), (Hough, 2014). Both the ventilatory support and MI-E are set to optimize the clinical treatment. Both pressure and duration settings may be individualized in MI-E. However, regarding how duration of the expelling phase of cough affects the expiratory flow, has not yet been systematically studied

To evaluate the efficacy of MI-E, Peak cough flow (PCF) has been the most used and preferred outcome (Chatwin et al., 2018). However, limitations of PCF have been described (Lacombe et al., 2019), (Lacombe et al., 2014) and other outcome measures have been introduced (Effective Cough Time (ECT) and Effective Cough Volume (ECV) (Lacombe et al., 2014), (Lacombe et al., 2019) but have not been compared to the established outcome measure; PCF.

We aim to test the feasibility of the study with healthy individuals, to uncover possible deficiencies, strengths and weaknesses of the protocol, instruments and outcome measures (Eldridge, Lancaster, et al., 2016). This aims higher methodical quality when we proceed to the future study (Eldridge, Lancaster, et al., 2016) testing individuals with neuromuscular disorders (NMD).

1.1 Personal introduction

My first introduction to mechanical ventilation and MI-E was when I worked as a physical therapist at the neuro - intensive care unit at Oslo University Hospital.

Later in my career, I started working at the Unit for Congenital and hereditary neuromuscular disorders. These disorders are many and the patient group is heterogeneous. In many of these disorders, the respiratory muscles are affected and the patients' ability to cough is hampered. In some disorders, both the respiratory muscles and the brain are affected, which both in turn may reduce the ability to cough.

As a physiotherapist, I have knowledge regarding pathological breathing patterns, symptoms of hypoventilation and symptoms of a weak and inefficient cough. Further, I can initiate respiratory support and/or assisted cough, and help the patients to gain a better function and increased quality of life. The ultimate aim is to tailor the individual MI-E treatment as effective as possible, making the patients spend as little time as possible when they perform the cough therapy.

In my clinical work, I discovered a lack of knowledge regarding how to titrate the expiration time in MI-E treatment. I wanted to systematically explore, in particular, MI-E setting in adults. The present study examining healthy individuals, will generate valuable information on how to conduct future studies in individuals with neuromuscular disorders.

1.2 Aims

The primary aim of the study was to assess the feasibility of the study methodology (protocol and pneumotachograph (Citrex H5, IMT medical, Buchs, Switzerland) and the feasibility of the outcome measures (PCF, ECT, ECV and self-perceived effect and comfort) as approaches to evaluate efficacy of MI-E when altering expiratory time.

The secondary aim was to compare the established outcome measure, PCF, with the novel outcome measures; ECT (Lacombe et al., 2014) and ECV (Lacombe et al., 2019), to investigate if the novel outcome measures could be more suitable evaluation tools when evaluating various exsufflation times.

1.3 Research questions and hypotheses:

Is the test protocol, the measuring instrument (pneumotachograph) and the outcome measures feasible to examine the impact of the expiration time on the efficacy of MI-E in healthy adults?

How does the expiration time impact the efficacy of MI-E in healthy individuals?

Are there any other outcome measures more suitable than PCF for assessing the effect of MI-E when changing the expiration time?

Research question 1:

Is the test protocol feasible in healthy adults?

Research question 2:

Is the measuring instrument feasible to measure PCF, ECT and ECV during MI-E in healthy adults?

Research question 3:

Are the outcome measures (PCF, ECT, ECV and self-perceived effect and comfort) feasible to evaluate the effect of MI-E when altering the expiration time in healthy adults?

Research question 4:

How does the exsufflation time (T_e) impact PCF, ECT, ECV and self – perceived effect and comfort?

Hypothesis 1:

#0 Longer exsufflation time (T_e) does not increase PCF

#1 Longer exsufflation time (T_e) increase PCF

Hypothesis 2:

#0 Longer exsufflation time (T_e) does not increase ECT

#1 Longer exsufflation time (T_e) increase ECT

Hypothesis 3:

#0 Longer exsufflation time (T_e) does not increase ECV

#1 Longer exsufflation time (T_e) increase ECV

Hypothesis 4:

#0 Longer exsufflation time (Te) does not increase the self – perceived effect

#1 Longer exsufflation (Te) increase the self – perceived effect

Hypothesis 5:

#0 Longer exsufflation time (Te) does not increase the self – perceived comfort

#1 Longer exsufflation time (Te) increase the self – perceived comfort

Research question 5:

Is there a correlation between PCF, ECT, ECV and the self – perceived effect and comfort?

Hypothesis 6:

#0 There is no correlation between PCF, ECT, ECV and the self – perceived effect and comfort.

#1 There is a correlation between PCF, ECT, ECV and the self – perceived effect and comfort.

1.4 Theoretical framework

The physiotherapists' field of knowledge is body, movement and function and the aim of a physiotherapy intervention is to improve or maintain a function (fysioterapeutforbund, 2012). In my clinical practice, I meet patients who feel they are dependent on the mechanical cough assistance to maintain the level of function and quality of life. Regularly MI-E treatment is required, sometimes several times a day, and may therefore be time consuming, resource demanding and tiring for the patients. Hence, the treatment should be both as gentle and

effective as possible. The results of this study on healthy adults will not be generalizable to the individuals with neuromuscular disorders. However, it will provide us with useful methodological information for a future study and may also challenge and modify our daily clinical practice (Domholdt, 2005).

A synergy of the theory of science and the biopsychosocial model (Engel, 1977) build the theoretical framework of this thesis. According to the World Health Organization and ICIDH-2, the definition of human functioning and disability is based on the integration of a medical and a social model. The medical model define disability as a personal problem and is directly caused by a trauma, disease or other health conditions that demands medical care provided by medical professionals. Management of the disability has the aim to cure, to adjust or change the consequences of the disability. The social model, on the other hand, look upon disability purely as a socially constructed problem. In other words, it is not an attribute of an individual, but rather a complex combination of conditions, many of which are created by the social environment (Organization, 2001).

In this study, we are exploring time settings on a mechanical cough device to investigate how the time settings impact the efficacy of MI-E in healthy adults. Even if the present study is of technical art, the results may contribute to form the future research with patients with the aim of individualizing and increasing the efficacy of MI-E treatment and further, increase function and quality of life. Consequently, this thesis should be read with the framework of the synergy of scientific and biopsychosocial theory, hand in hand with the understanding of function and the physiotherapeutic aim to improve or maintain a function.

2. Background

2.1 Neuromuscular disorder

Neuromuscular disorders encompass a diverse group of disorders, which affect the motor units (Hutchinson & Whyte, 2008). A motor unit consists of the motoric nerve cell in the dorsal horn, the peripheral axon, the axons terminal branches, the associated neuromuscular junctions and the muscle fibers the nerve cell supplies with impulses (Ciafaloni, Chinnery & Griggs, 2014). Most neuromuscular disorder have a prevalence between 1 and 10 in 100 000 (Deenen, Horlings, Verschuuren, Verbeek & van Engelen, 2015).

Although neuromuscular disorders may include a large variety of disorders, they are divided into inherited or acquired disorders, predominately manifesting with motor dysfunction (Voulgaris, Antoniadou, Agrafiotis & Steiropoulos, 2019).

Neuromuscular disorders are a heterogenous group regarding onset of disease, degree of respiratory failure and course of disease. The degree of weakness may vary and depends on the disorder (Hutchinson & Whyte, 2008). Any generalized neuromuscular disorder which becomes severe may, in theory, involve the respiratory muscles (Hutchinson & Whyte, 2008).

2.2 Respiratory muscles

The lungs hang from whichever part of the chest wall is uppermost at the time and are attached to each other medially by their roots. They do not directly touch any muscle. The chest wall comprises the thoracoabdominal wall and diaphragm. The diaphragm contracts downwards against the abdominal contents, which are themselves incompressible, and the rigid pelvic bowl (Hough, 2014).

The respiratory muscles extend from the mastoid process to the pubic symphysis and are the only skeletal muscles vital to life, providing the power for the respiratory pump and delivering oxygen to the distal airways while removing CO_2 (Hough, 2014).

2.2.1. Inspiration

According to the Greeks, the diaphragm is the seat of the soul and is a dome-shaped sheet of muscle on which the upright lungs rest, separated by the pleura and generates 70% of the tidal volume (Hutchinson & Whyte, 2008). Other muscles assisting in the inspiratory process

during increased work of breathing (airflow obstruction or exercise), are the external intercostals, the scalenes and the pharyngeal muscles (Hough, 2014).

2.2.2 Expiration

There is a smooth transition between inhalation and exhalation because of a brake of expiratory flow caused by airflow resistance, especially at the larynx, and by continued low-grade diaphragmatic activity (Hough, 2014).

Normal exhalation is more or less passive with lung elastic recoil providing the driving force. However, when speaking, coughing, sneezing etc., the active expiration becomes stronger and the abdominal muscles, internal intercostal muscles and the pelvic floor muscles may then be recruited to augment passive recoil (Hough, 2014).

2.2.3 Respiratory muscles weakness

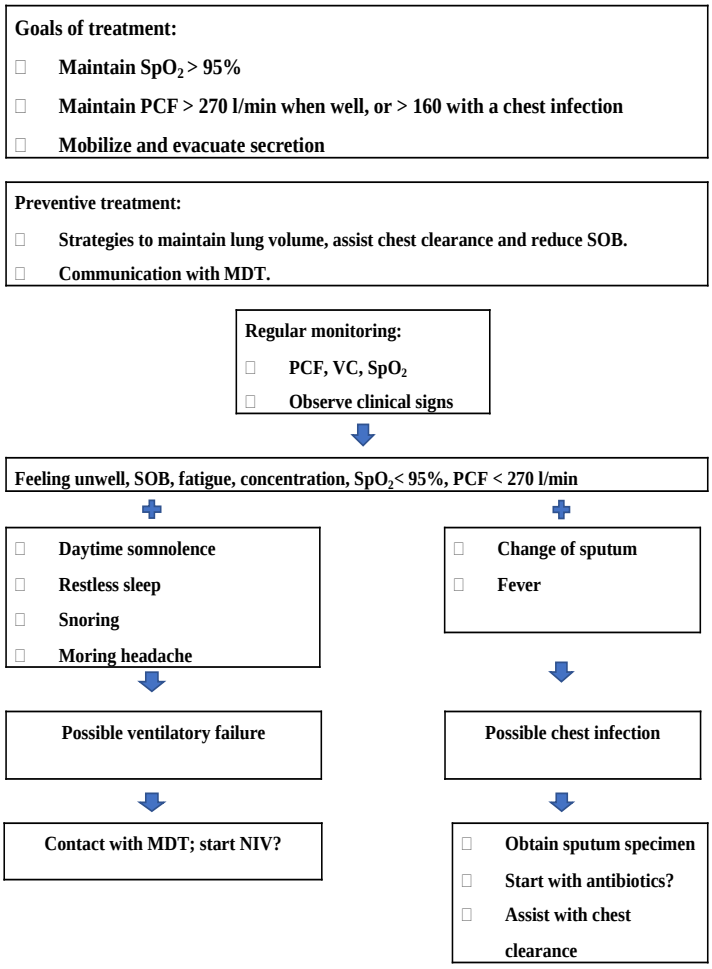
Weak inspiratory muscles cause a restrictive disorder by limiting lung expansion (Hough, 2014). The inability to fill the lungs with air will cause reduced inspiratory volume as well as expiratory flow, which is necessary to be able to cough and clear the airways (Chatwin et al., 2003). Weak expiratory muscles impair the cough and clearance of the airways (Hough, 2014). Without the ability to clear the airways there will be a high risk of pneumonia and acute respiratory failure (Ambrosino, Carpene & Gherardi, 2009), (Bach et al., 1997). Most patients do not realize the extent of their respiratory muscle weakness until the they experience complications. Ventilatory failure can arrive unexpectedly if respiratory weakness goes undetected. Regularly monitoring of lung function, to be able to detect symptoms of hypoventilation (pCO_2>6.0 kPa) and ventilatory failure, are therefore important to prevent. acute respiratory failure and hospitalization (Hough, 2014).

2.2.4 Neuromuscular disorders with respiratory muscle involvement

The respiratory muscle involvement in NMD may differ. In Spinal Muscular Atrophy type 1 there is a universal respiratory muscle involvement and it occurs to a variable extent in type 2 and 3 (Hutchinson & Whyte, 2008). In Congenital Myopathies respiratory muscle involvement is best recognized in Nemaline Myopathy, Myotubular Myopathy and Multiminicore Disease, and the respiratory failure is often evident in the neonatal period. However, in a rare variant of Nemaline Myopathy the onset of respiratory weakness occurs in adult life (Hutchinson & Whyte, 2008). Respiratory failure is often common in Congenital

Muscular Dystrophy and is often fatal in childhood or the second decade (Hutchinson & Whyte, 2008). In Dystrophinopathy as Duchenne muscular dystrophy (DMD), the weakness of the respiratory muscles is universal but is less common in Becker muscular dystrophy. Myotonic dystrophy is a multisystem disorder and respiratory failure, pneumonia or cardiac conduction defects are common causes of death. Furthermore, these patients can also have a central defect of respiratory control (Hutchinson & Whyte, 2008). In Limb Girdle Muscular Dystrophy respiratory muscle weakness is particularly associated with type 2C, 2D, 2E and 2F and is also seen in 2I. In mitochondrial myopathy respiratory involvement is well-recognized, and in Myasthenia Gravis weakness of the bulbar and respiratory muscles is the most serious complication (Hutchinson & Whyte, 2008).

Figure 1. Flow chart showing how to monitor and manage patients with neurological disorders and potential ventilatory failure:



Abbrevations: MDT: multidisciplinary team including neuro-physical therapist, NIV: non-invasive ventilation, PCF: peak cough flow, SOB: shortness of breath, VC: vital capacity (Hough, 2014).

2.3 Normal cough

"*A cough is only as effective as the deep breath preceding it.*"

Sobush (Sobush, 2008)

The cough is the body's strongest physiological reflex (Hough, 2014). The ability to cough is crucial to be able to clear the airways. A normal cough is a dynamic function and consists of three main phases (Voulgaris et al., 2019):

1. The inspiratory phase; a deep inhalation.
2. The closing phase; where the throat closes to increase the intrathoracic pressure.
3. The expiratory/pressure phase; after opening the throat and the airflow increases and mobilizes the secretion.

Normal cough consists of an initial inspiratory phase (1.) to reach a lung volume 80 – 95 % of total lung capacity. In the closing/compression phase (2.) there is rapid closure of the throat/glottis for 0. 2 seconds with simultaneous contractions of the expiratory muscles, to create a pressure greater than 200 cm H_20. In the expiratory/expulsion phase (3.) there is a rapid opening of the throat/glottis while the expiratory muscles continue to contract in order to produce an expiratory cough flow greater than 400 L/min (Voulgaris et al., 2019). High expiratory flow is essential to remove secretion and clear the airways (Voulgaris et al., 2019), (Finder, 2010), (Volpe, Naves, Ribeiro, Ruas & Amato, 2018), (Chatwin et al., 2003). Therefore, impairment of the inspiratory, the expiratory or glottis muscles of people with neuromuscular disorders may compromise the ability to cough efficiently, and may lead to respiratory failure.

2.4 Peak cough flow

Peak cough flow (PCF) is widely considered to evaluate the ability to cough and predict cough efficiency in patients with NMD (Chatwin et al., 2018). It is the peak value of the maximum airflow during the expiratory phase when coughing, and it works as an indicator of

the ability to mobilize secretion in the airways. An airflow meter can easily measure PCF by coughing into it. The PCF value occurs quickly after the throat has opened, during the expiratory phase of the cough. When PCF is less than 270 l/min the ability to cough and clear the airways is reduced in patients with NMD. The risk of pulmonary complications, such as pulmonary infections or acute respiratory failure, will be high and indicates a need for mechanical cough assistance. The cough efficiency and the ability to clear the airways is highly impaired at PCF 180 l/min and less efficient (Chatwin et al., 2018).

2.5 Pulmonary physiotherapy

Airway infections are the main cause of hospitalization in patients with neuromuscular disorders (Jung et al., 2018). Pulmonary physical therapy and non-invasive ventilation and cough assistance are therefore vital interventions for this patient group (Chatwin et al., 2018). It is shown that cough assistance in both the inspiratory and the expiratory phase can reduce the risk of pulmonary infections and hospitalization (Bach et al., 1997), (Jung et al., 2018), (Chatwin et al., 2003).

Neuromuscular patients experience secretion retention due to inability to cough and clear the airways effectively, but they may also experience reduced inspiratory volume and increased work of breathing (WOB). These are typical complications that physiotherapy may act on, with the goal to support and improve function. Aiming to assist clearance of secretion, both manual and mechanical support is used to support the cough. To increase volume both breath-stacking of lung recruitment can be used and a balance of rest and exercise is recommended to reduce work of breathing (Hough, 2014).

2.6 Mechanical insufflation – exsufflation (MI-E)

Norwegian national guidelines recommend mechanical cough assistance when the cough flow declines to <270l/min (Aarrestad S., 2012). The mechanical cough assist uses a technique called Mechanical insufflation – exsufflation (MI-E), and deliver a positive pressure during inspiration (insufflation) and a negative pressure during expiration to empty the lungs for air (exsufflation). Alternate insufflation – exsufflation is simulating a normal cough cycle and will in that way give support to the patients' weak cough efficiency. MI-E has shown to increase PCF and by that improve the ability to cough and to clear the airways (Ambrosino et al., 2009), (Chatwin et al., 2003), (Bach et al., 1997), (Jung et al., 2018), (Lacombe et al.,

2014), (Hov et al., 2020). Settings for in- and exsufflation pressure, how the inspiratory pressure increases i.e. rise time/inspiratory flow, insufflation time and exsufflation time are individually adjusted on the device. Either the patient can trigger the machine to start the cough cycles or, if the patient is too weak to trigger, the device can be set on Auto-mode to start the cough cycles automatically. The range of the possible setting alternatives are listed in Attachment 1.

According to the National registry of long - termed mechanical ventilation report for 2020, approximately 1600 individuals with NMD have established treatment in Norway since 2002 and about 50% still receive ventilatory support (Fondenes, 2021). In 2010 the national prevalence of long - term mechanical ventilation was 26.5 / 100 000 (Fondenes, 2021). 244 individuals have over the last five years commenced ventilatory treatment whereof approximately 30% are individuals with NMD (Fondenes, 2021). In some NMD children one of three with NMD is equipped with a MI-E device for long – term use (Hov et al., 2021).

2.7 MI-E increases PCF

Safety and effect of MI-E was summarized in a systematical review from Morrow et al. (2013) (Morrow, Zampoli, van Aswegen & Argent, 2013). In five studies including a total 105 participants, they found that MI-E is improving PCF and the ability to clear the airways. However, the MI-E did not increase PCF significantly more than other cough augmentations methods studied (Morrow et al., 2013). Further, they found that the optimal settings for pressure, treatment frequency and settings for insufflation – exsufflation time in MI-E is unknown and that there is a need for further research for optimal settings in MI-E (Morrow et al., 2013).

Chatwin et al. (2003) hypothesized that treatment with MI-E would increase PCF more than other cough augmentation techniques in individuals with NMD (Chatwin et al., 2003). The pressure was titrated according to the patients' comfort. However, the insufflation and exsufflation time was not specified. The average pressure was measured in the mask and showed 15±3 cmH_2O and -15±9 cmH_2O. A statistically significant increase of PCF was reported during MI-E. The increase showed 235±111 l / min (Chatwin et al., 2003).

Jung et al. (2018) assessed the improvement of PCF using MI-E treatment in patients with NMD hospitalized with pneumonia (Jung et al., 2018). In this study he used respectively pressures of +40cmH_2O/-40cmH_2O with 2-3 seconds insufflation time and 1-2 seconds

exsufflation time. The patients completed 5 cough cycles. To avoid hyperventilation there were pauses of 20-30 seconds between the cycles. This study showed a significant increase of PCF after MI-E treatment. It also showed an increase after 15 and 45 minutes. However, there were no significant difference between 15 and 45 minutes (Jung et al., 2018).

Sivasothy et al. (2001) assessed the effect of manual cough assist and mechanical insufflation, and did not find an increase of PCF with mechanical insufflation alone (Sivasothy, Brown, Smith & Shneerson, 2001) However, they did find a significant increase of PCF with manual cough assist and mechanical insufflation in combine. The pressure settings were 20 cmH_2O and -20 cmH_2O. There were two breathing cycles and at the third cycle, the patients were instructed to cough as hard as possible without exsufflation. No insufflation time or exsufflation time was specified (Sivasothy et al., 2001).

Lacombe et al. (2014) compared the effect of mechanical insufflation in combination with manual cough assist, MI-E alone and MI-E in combination with manual cough assist in patients with neuromuscular disorders (Lacombe et al., 2014) It showed that PCF was at the highest with mechanical insufflation in combination with manual cough assist (MAC) (Lacombe et al., 2014). The insufflation pressure and exsufflation pressure was gradually increased/decreased to the highest/lowest tolerable pressure; 40 cmH_2O/-40 cmH_2O. Neither insufflation pressure nor exsufflation pressure was specified (Lacombe et al., 2014).

Hov et al. (2020) used a pediatric lung model and adjusted the settings in MI-E gradually and found that a plateau of the expiratory airflow curve was reached when; a) the exsufflation pressure was -40 or -50 cmH_2O, b) the insufflation time was more than 1 second and c) at an insufflation pressure from 35 cmH_2O (Hov et al., 2020). This showed that the expiratory pressure affects the expiratory airflow more than the inspiratory pressure and time do. The expiratory airflow ceased after half a second and there was no difference in PCF when increasing the exsufflation time to more than 1 second. Based on these findings, they suggested basic settings when titrating MI-E settings in children with neuromuscular disorders; inspiratory and expiratory pressure with respectively 20 and 30 cmH_2O and -40 cmH_2O and an inspiratory time of more than 1 second. However, more studies are needed to confirm these findings (Hov et al., 2020).

In an observational longitudinal cross-sectional study, Chatwin and Simonds (2020) followed 181 MI-E users for 4 years to inspect what settings they used (Chatwin & Simonds, 2020). On average, they found that the exsufflation pressure was higher than the insufflation pressure with approximately 10 cm H_2O and that the insufflation time was shorter than the exsufflation

time. The setting for insufflation flow i.e. rising - time was defined as «high» (Chatwin & Simonds, 2020).

The anatomical and physiological conditions in children and adults are different. Adults have bigger and more stable airways, higher tidal volumes and lower respiratory frequency. However, neuromuscular disorders can affect the respiratory muscles and because of this the compliance in the lungs in adults, can be reduced (Morrow et al., 2013). This means that the elasticity of the lung tissue is reduced and that there's a risk for damaging the lung tissue when using high positive pressures in MI-E. Although adults have a higher tolerance for high positive pressures than children do, the aspects of effect and security are crucial when changing the MI-E settings both in adults and children (Morrow et al., 2013), (Hov et al., 2020).

There has been little focus on time settings for mechanical cough assist in studies. The insufflation time has been shown to be important (Hov et al., 2020). However, the effect of exsufflation time in adults with neuromuscular disorders has not been systematically assessed. The aim of this feasibility study was also to investigate this systematically in healthy adults.

2.8 An interest for other outcome measures for efficacy in MI-E

2.8.1 Peak Cough Flow

According to Branson (2020), Barach and co –workers noticed the importance of PCF in identifying patients who might benefit from MI-E and for monitoring MI-E success already in the 1950th (Branson & Benditt, 2020).

Although PCF is the most common outcome measure used to assess cough efficiency, it has known limitations. PCF shows only a peak value of the expiratory airflow. This value occurs rather fast; within the first 100 milliseconds when the mechanical cough assist changes from insufflation to exsufflation (Lachal, Louis, Subtil & Guerin, 2019). A normal exsufflation time is from 0.5 seconds and up to 4.0 seconds and is often adjusted, from clinical experience, to be longer than the time PCF occurs. Because PCF does not take the time aspect of the exsufflation phase into account, we suggest that it may be a limited outcome measure to evaluate the effect of exsufflation time.

2.8.2 Effective Cough Time

The study of Lacombe et al. (2014) introduced a new possible outcome measure with a time aspect for cough efficiency and evaluation of effect of MI-E (Lacombe et al., 2014) The term Effective cough time (ECT) was introduced for the first time in this study, and defined as the time PCF is above 180 l/min (Lacombe et al., 2014), measured in seconds. ECT may indicate the time the PCF value is at a level secretion can be mobilized.

2.8.3 Effective Cough Volume

Lacombe et al. (2019) also introduced the term Effective cough volume (ECV) and defined this as volume (liters) expired, but only measured when the PCF is >180 l/min (Lacombe et al., 2019). In this study it was also found that ECV was more sensitive than PCF for discovering upper airways collapse during exsufflation (Lacombe et al., 2019). Neither ECT nor ECV has been used to evaluate the effect of MI-E in other studies.

Our hypothesis was that ECT and ECV, in particular, will help us to a greater extent help us evaluate the effect of the mechanical cough assistance when altering the expiration time. We also wanted to investigate the correlation between the different outcome measures for effect (PCF, ECT, ECV and the participant's self-perceived effect and comfort).

3. Methods and materials

3.1 Design

This present study is a quantitative feasibility study with an explorative cross - sectional design.

A feasibility study is often conducted to inform a future study (Eldridge, Lancaster, et al., 2016) and is typically used when there is little knowledge about the research area (Kumar, 2011). A small – scale study is undertaken to decide if it is worth carrying out a detailed investigation (Kumar, 2011). A feasibility study is helpful to investigate areas of uncertainty, for example in instruments, the test protocol and in exploring potential outcome measures (Eldridge, Lancaster, et al., 2016). Assessing feasibility in this way ensures that fewer problems are likely to be encountered in future studies. Furthermore, this encourages methodological rigor and higher quality in the subsequently following main studies. The intention is that by resolving points of uncertainty at an early stage, the ultimate study is more likely to succeed (Eldridge, Lancaster, et al., 2016).

3.2 Subjects and sample size

As this present study is a feasibility study, a formal sample size calculation was not required (Eldridge, Lancaster, et al., 2016), (Eldridge, Chan, et al., 2016). In total, 20 healthy volunteers working at Haukeland University Hospital (HUS) was included. The participants were a convenience sample (Blaxter, Tight & Hughes, 2010) of volunteering colleagues from the clinic and members of our research team. To prevent participants from feeling pressured to participate, the recruitment manager ensured to recruit more peripheral colleagues. The participation was voluntary and the participant could, at any time withdraw from the study.

Before inclusion, the participants were screened for the following exclusion criteria's; ongoing airway infection, obstructive pulmonary disease and not vaccinated against Covid-19.

3.3 Testing procedure

3.3.1 Preparations

Before examination we informed the subjects about the study; storage and deletion of the data, the testing procedure and what they could expect.

While the research physical therapist informed, registered and examined the subjects, the research assistant prepared the mechanical cough device, the pneumotachograph (CitrexH5, IMT medical, Buchs, Switzerland) and ensured a randomized order (Urbaniak, 2013) of the time setting for each subject.

3.3.2 Baseline data

At baseline the characteristics of the study population; date of birth, sex, height and weight was registered and BMI was calculated.

3.3.3 Pulmonary function

Examination of pulmonary function was performed prior to the MI-E intervention.

Spirometry was performed in a sitting position and according to guidelines of The American Respiratory Society and the European Respiratory Society (Graham et al., 2019). Forced vital capacity (FVC), Forced expiratory volume first second (FEV_1) and Peak Expirtory Flow (PEF) were measured with a desktop spirometer (Microlab, Vyaire Medical Inc, Mettawa, IL)

and were reported as percentage of predicted according to reference values of GLIO (Quanjer et al., 2012). Peak Cough Flow was measured with a hand – held peak flow meter (Vitalograph, Ennis, Ireland).

Respiratory muscle strength; Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) was also measured in a seated position and according to the statement of The American Respiratory Society / European Respiratory Society (ATS / ERS) (2002) (American Thoracic Society/European Respiratory, 2002) and was measured with a respiratory pressure meter Micro RPM (Micro Medical Ltd, Rochester, England) and were reported as predicted.

The highest value of three attempts were recorded.

3.3.4 MI-E intervention

The participants who weren't familiar with the mechanical cough assist device, had the opportunity to try it and get to know it before starting the testing procedure. We used the same mechanical cough assist device on all the subjects (Cough Assist E70, Respironics, Murrysville, PA). However, we used an extra filter to protect both the machine and the participants and we changed the filters and mask between every participant. The testing procedure was conducted with the participant sitting in a chair. The mask was connected to a filter, an adapter, a pneumotachograph and a 22 mm circuit hose. The mask was carefully placed over the mouth and nose to avoid leakage. The testing procedure was conducted according to the standard protocol and by the research physical therapist and we tried to adjust it so that there was as little strain as possible for the participants at all times. The subject was instructed to cough during exsufflation.

The settings on the mechanical cough assist:

-Insufflation pressure: +40 cmH2O

-Exsufflation pressure: -40 cmH2O

- Trigging of Insufflation: ON

- Insufflation flow: High

- Insufflation time: 2.5 seconds

Exsufflation times (T_e) used in randomized order were as follows: 0.5 sec / 1.0 sec / 1.5 sec / 2.0 sec / 2.5 sec / 3.0 sec / 3.5 sec / 4.0 sec. The maximum exsufflation time was therefore sat to 4.0 sec, as this is the longest duration on exsufflation time used in previous studies.

3.3.5 Randomization and blinding

The order of the exsufflation times was randomized. The research assistant used a digital randomization tool (Urbaniak, 2013) that provided 20 random orders of the exsufflation times; one random order for each participant. The test was double blinded; neither the patient nor the research physiotherapist knew the order of the exsufflation times (Aalen & Frigessi, 2018). The research assistant set the mechanical cough assist and the research physical therapist ensured correct position of the mask and the hose during testing.

Figure 2. MI-E intervention. Research physiotherapist testing one of the subjects. The research physiotherapist is holding the pneumothacograph with the tube and filters and the subject gives support to the mask to avoid air leakage. Consent for publishing this photograph was given from the participant.

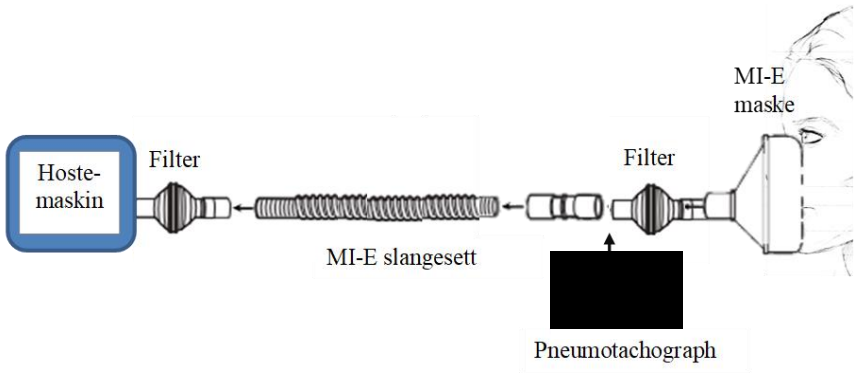
Each participant went through 6 cough cycles of each time setting. To avoid hyperventilation of the participants, there was a minimum 30 seconds break between each setting (Hough, 2014), (Jung et al., 2018).

3.3.6 Registration of airflow and pressure during MI-E intervention

The airflow and -pressure were registered during the MI-E cycles. A high-end Ventilator Tester including both pneumotachograph and pressure transducer (CitrexH5, IMT medical, Buchs, Switzerland) was placed between the facemask and ventilatory circuit for Cough Assist E70 to measure flows, volumes and pressures during the interventions with MI-E (Figure 3). Signals were digitalized, sampled and run on computer with appropriate software (FlowLab, Buchs, Switzerland). Data were further stored as Excel files (Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, Washington, USA) and thereafter constructed

to synchronized airflow- and pressure curves to Acknowledge Software 4.2 (East Palo Alto, USA).

Figure 3. Pneumotachograph



The pneumotachograph was placed between the mask and the adapter of the mechanical cough assist.

3.3.7 Measurements of self-perceived effect and comfort

The research physiotherapist asked the participant their opinion of the effect and comfort just after each time setting by using the Visual Analog Scale for evaluating Dyspnea (VAS) 0-10 (Foglio et al., 1999). The Visual Analog Scale consist of a horizontal line of 100 mm with numbers to evaluate self-perceived effect and comfort (Foglio et al., 1999). The respondents marked the scale, which is scored by measuring the distance from the lower end of the horizontal line to the mark. The score 0 means “no effect” and “very uncomfortable”. Reliability and validity of the VAS have been reported (Foglio et al., 1999).

3.4 Calculations of PCF, ECT and ECV

After the completed data collection, values of PCF, ECT and ECV were extracted from the synchronized airflow- and pressure curves at the Acknowledge Software 4.2. PCF values on each MI-E cycle were registered from the maximum values on the exsufflation flow curve when the pressure curve indicated an exsufflation phase. To calculate the ECT and ECV, a duplicate of a flow curve was created. This second flow curve got a modified zero-level; set on 180 l/min on the exsufflation flow. Both the Delta Time and Integral values were extracted during the exsufflation phases on all MI-E cycles in the following way: for every time setting (T_e), the curve / length of expiration phase was marked manually. To ensure accuracy of the

registrations we verified the beginning of the expiration curve with the pressure curve, and we verified the time with the Delta T value. This process made it possible to register the ECT, and to calculate ECV; Integral : 60 = ECV. The process was based on personal communication with Matthieu Lacombe, that have launched these outcome values.

3.5 Analyses and data management

As this is a feasibility study, data pertaining the primary aims was reported by using descriptive statistics (Thabane et al., 2016).

Characteristics of the study and the examination of the pulmonary function was presented in descriptive statistics. Categorical values were presented as count and percentages. Due to a small sample and a violation of the assumption of a normal distribution of the PCF values, continuous variables were presented as median (min-max).

A box plot graph was used to visually demonstrate the spread of the scores in the distribution, including range, median and interquartile range. The boxes represent the interquartile (25-75 percentile) range, which represents the spread of values within the middle 50% of the data, and the horizontal line inside the box is the median. The whiskers represent the range of the values (Portney, 2020).

Additional analyses of differences in effect in a feasibility study were not applicable because the primary focus was not on determining treatment effects, rather the focus was on assessing feasibility to inform the design of the future study (Eldridge, Chan, et al., 2016). However, to determine feasibility of the outcome measures PCF, ECT, ECV and self-perceived effect and comfort, we needed to explore the relationship between T_e and the outcome measures. Before performing a correlation analysis between Te, PCF, ECT and ECV a scatterplott Matrix was generated. This to ensure no violation of the assumptions of linearity (Pallant & Pallant, 2020).

Due to violation of the assumption of a normal distribution of the PCF values correlations between Te and PCF / ECT / ECV were assessed by Spearman Rank Order Correlation (rho). The p - value is expressing the probability that the found correlation is due to chance. If the level of significance is set to 0.05 there is a 5% probability that the found correlation occurred by chance alone. It means that 5 out of 100 found correlations is due to chance. In this study level of significance is set to .05 (Portney, 2020).

The results of a correlation assessment may range from -1 to +1 (Pallant & Pallant, 2020). A correlation of 0 indicates no relationship, a correlation of 1 indicates a perfect positive

correlation, and a value of -1 indicates a perfect negative correlation. To interpret the strength of the values of 0 and 1, Pallant referes to Choen (1988) who suggests following guidelines: There is a small correlation with *r* from .10 to .29, a moderate correlation with *r* from .30 to .49 and a strong correlation with *r* from .50 to 1.00 (Pallant & Pallant, 2020).
Data from the examination were stored in separate registration forms where all participants had a unique participant number. The data was in that way anonymized and stored and processed both in Excel and SPSS for Windows, (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp where SPSS were used for the statistical analyzes.

3.6 Missing data

Missing data was investigated and handled with the use of imputation. Because of the small sample size we imputed the median value at the respective time setting T_e (Portney, 2020).

3.7 Validity and reliability of the study

Assessing quality of a study is an important aspect in all research. (Laake, Olsen & Benestad, 2008).

3.7.1 Validity

Sttistical conclusion validity concerns the appropriate use of statistical procedures for analyzing data, leading to conclusions about the relationship between independent and dependent variable (Portney, 2020). Statistical power, violation of assumption of statistical tests and reliability and variance are some of the threats to statistical conclusion validity (Portney, 2020).

Validity of the measurements indicates to what extent the test and / or instrument measure what it is supposed to measure (Pallant & Pallant, 2020). Internal validity focuses on cause-and-effect relationship and this relationship can be threatened by events or changes that occur during a study (Portney, 2020). Confounding variables and instrumental effects are some of the threats to internal validity. Construct validity related to design concerns how variables are conceptualized and how well experimental results can be generalized within the desired clinical context (Portney, 2020). External validity refers to the extent to which the results of a

study can be generalized, and may be threatened by interaction of treatment with the type of subjects tested, setting and time of history when the study is done (Portney, 2020).

3.7.2 Reliability

Reliability is fundamental to all aspects of measurements and it refers to the extent to which a measured value can be obtained consistently during repeated assessment of unchanging behavior (Portney, 2020).

According to classical measurement theory, any observed score consists of an error component and a true score. Reliability can therefore be defined as an estimate of the extent to which an observed test score is free from error or how well observed scores reflect true scores (Portney, 2020). Measurement errors may be caused by the individual taking the measurement, the measuring instrument and the variability of the characteristics being measured (Portney, 2020).

Rater reliability is important whether one or several testers are involved. Intra-rater reliability refers to the stability of data recorded by one tester across two or more trials. Inter-rater reliability concerns variation between two or more raters who measure the same subjects (Portney, 2020).

3.8 Ethical aspects

The volunteers had to spend an hour of their spare time being tested, and some of them experienced the testing procedure as a bit uncomfortable. However, most of the participants expressed that the examination was rather exciting and gave them knowledge about how the patients might experience the MI-E treatment. The testing procedure was considered as safe and with minimal risk and discomfort to healthy subjects with no respiratory problems.

This project was approved by the Regional Comitee of Medical Research Ethics (Regionale komiteer for medisinsk og helsefagligforskningsetikk, reference number 182325). Initially, in this study the plan was to test individuals with neuromuscular disorders. However, because of Covid-19 and the following restrictions we didn’t want to take the risk and expose them for unnecessary testing. We thus decided to conduct a feasibility study on healthy individuals first to increase the quality of the following study. The present study was approved by Regional Comitee of Medical Research Ethics after sending a change message with application to expand the total study population with a healthy control group.

All participants received verbal and written information about the study and gave their written informed consent to participate in the study and for publication of the results. Signing the consent statement was voluntary and the participants could, at any time and without a reason, withdraw from the study.

A codelist of names with an individual specific number was stored separately from the data. The data were saved and stored on a secured research server at Haukeland University Hospital (HUS).

3.8.1 Covid-19

The guidelines for conducting the tests followed the national guidelines from Folkehelseintituttet (FHI) / local guidelines at Haukeland University Hospital (HUS). During testing of the pulmonary function and the testing procedure, we tried to keep a distance of 1 meter to the participant and between us researches. We changed the mask and filter and disinfected all surfaces of the device between each participant. We also used an extra filter in the circuit to protect both the participant and the equipment.

4. Results

4.1 Subjects

In total 20 healthy volunteers, whereof 65% women and 35% men (table 1), were tested. Age of this study sample was between 25 and 65 years (table 1). The median age was 40.5 years.

4.2 Protocol

20/20 (100%) completed the test protocol including implementation of the MI-E intervention. However, because of a design error of the questionnaire of self – perceived effect and comfort, the study protocol was not shown feasible.

4.3 Measuring instrument

The pneumotachograph (Citrex H5, IMT medical, Buchs, Switzerland) registered the flow and pressure values during all dynamic MI-E cycles on all Te settings. The data was successfully transferred to the software Acknowledge, where we could extract the PCF, ECT and ECV values for analyses. Of total PCF values, 32.3 % had the same flow value of 300 l / min.

4.4 Descriptive statistics

4.4.1 Baseline characteristics and pulmonary function

Values of FEV1, FVC and cough - PEF were within the normal values (table 2) (Quanjer et al., 2012), (Bianchi & Baiardi, 2008).

Table 1. Baseline characteristics of the study participants

Variables	Total number=20 (100%)	Females=13 (65%)	Males=7 (35%)
Age, years	40.5 (25– 65)	32 (25 – 52)	53 (27 – 65)
Height, cm	175 (156 – 194)	170 (155 – 177)	182 (174 – 194)
Weight, kg	73 (53 – 158)	68 (53 – 75)	86 (64 – 98)
BMI, kg/m^2	24 (19 -29)	23 (19 – 27)	26 (21 – 29)

Abbreviations: Body mass index (BMI). All variables continuous and are reported as median and (min-max).

Table 2. Pulmonary function

Variables	Total number, n=20 (100%)	Females, n=13 (65%)	Males, n=7 (35%)
FEV1, liter	3.4 (2.2 – 5.4)	3.2 (2.2 – 4.0)	4.1 (3.4 – 5.4)
FVC, liter	4.2 (3.0 – 6.7)	4.1 (3.0 – 4.3)	5.4 (4.6 – 6.7)
PCF l/min	385 (260 – 600)	365 (260 – 445)	515 (385 – 600)
MIP, cmH_2O	-99 (-64 – -151)	-95 (-64 – -143)	-124 (-70 – -151)
MEP, cmH_2O	146 (73 – 248)	134 (73 – 198)	152 (103 – 248)

Forced expiratory volume first sec (FEV1), Forced vital capacity (FEV), Peak cough flow (PCF), Maximum inspiratory pressure (MIP), Maximum expiratory pressure (MEP). All variables are continuous and are reported as median (min – max).

4.4.2 Self – perceived effect and comfort

All 20/20 scored the Visual Analog Scale (VAS) for evaluating the self – perceived effect and comfort after every time setting. However, the questionnaire of self – perceived effect and comfort failed to capture the VAS scores after every cough cycle and the questionnaire of self – perceived effect and comfort is therefore not feasible.

4.4.3 Peak Cough Flow and Exsufflation time

The clustered box plot and histogram of Peak Cough Flow and Exsufflation time shows a roof effect of PCF values (Figure 4 and 5). The clustered box plot also shows several outliers mainly in males but four in females as well and further, extreme values in males (figure 4).

The histogram shows that the majority of males reached the maximum possible measured values and thus reached a roof effect. Although females do not show the same roof effect, there are small differences in PCF when altering the T_e (figure 5).

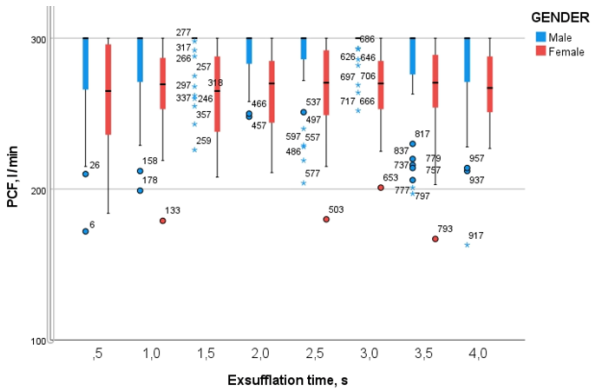


Figure 4. Clustered box plot of Peak Cough Flow and time. Reported as median.

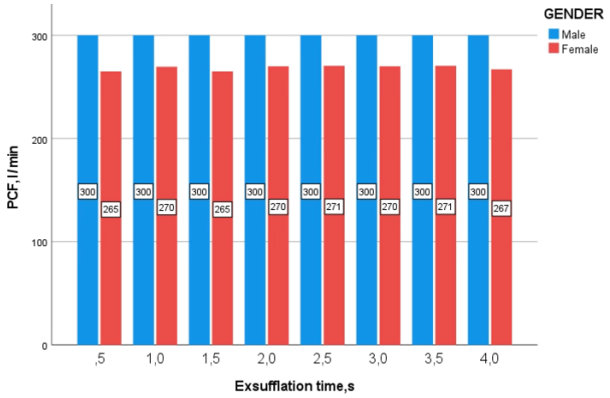


Figure 5. Histogram of Peak Cough Flow and exsufflation exsufflation time. Reported as median.

4.4.4 Effective cough time and Exsufflation time

This clustered box plot of Effective Cough Time and Exsufflation time shows a wider range of values in the male distribution and it also reveals outliers both in females and males and detects two extreme values in males (figure 6).

The histogram of Effective Cough Time and Exsufflation shows small differences in the increase of Effective Cough Time when altering the T_e and there is still an increase at T_e 4.0 sec in both females and males (figure 7).

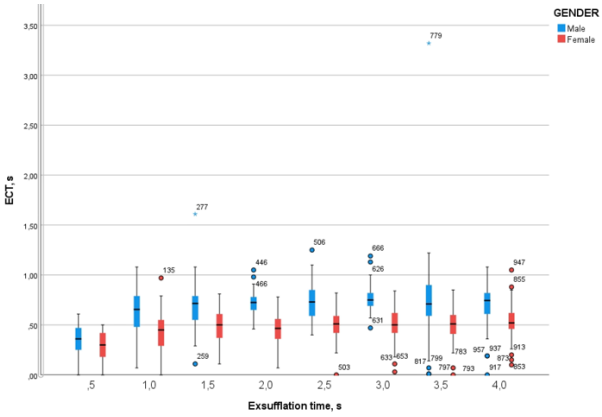


Figure 6. Clustered box plot of Effective Cough Time and Exsufflation time. Reported as median.

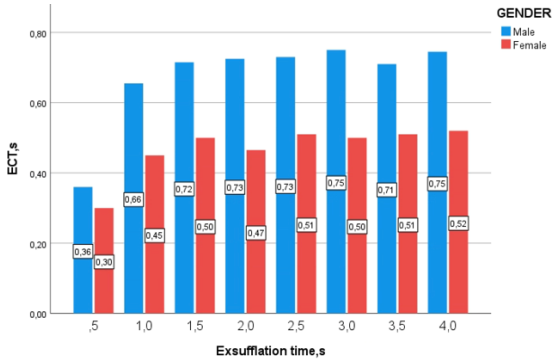


Figure 7. Histogram of Effective Cough Time and Exsufflation time. Reported as median.

4.4.5 Effective cough volume and Exsufflation time

The clustered box plot of Effective cough volume and Exsufflation time show a wide range of values in the male distribution (figure 8). The clustered box plot also shows three outliers, one in males and two in females (figure 8). The histogram shows an increase of ECV in females until T_e 4.0 sec and shows a plateau of increase of ECV in males at T_e 3.0 sec in males (figure 9).

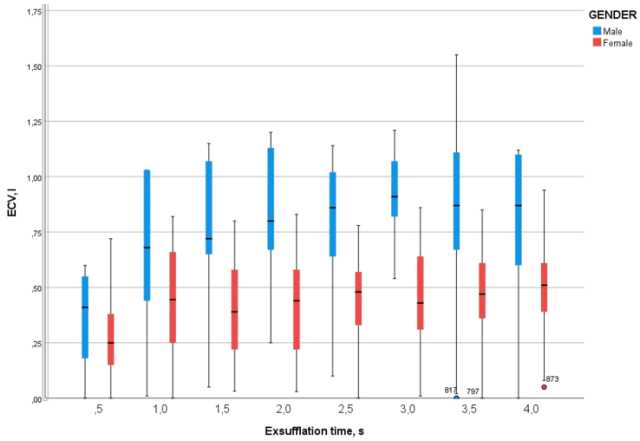


Figure 8. Clustered box plot of Effective Cough Volume and Exsufflation time. Reported as median.

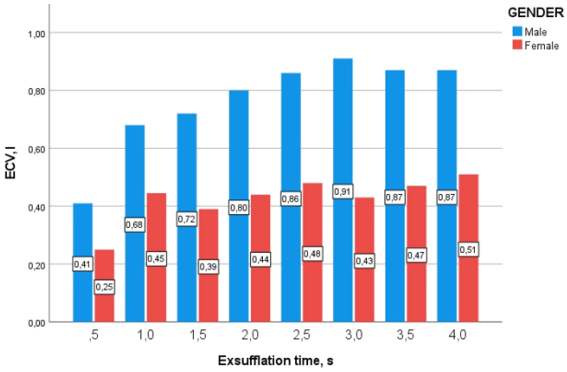


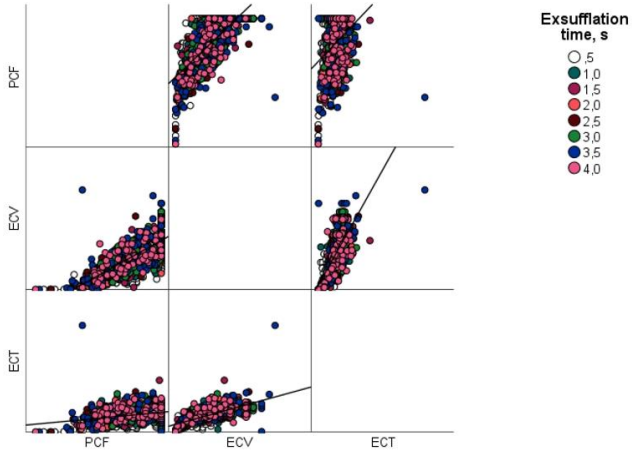
Figure 9. Histogram of Effective Cough Volume and Exsufflation time. Reported as median.

4.5 Association between outcome measures

4.5.1 Preliminary analysis for correlation

The scatterplot matrix meets the assumption of linearity and show positive correlations. It also illustrates the roof effect well found in PCF (figure 10).

Figure 10. Scatterplot Matrix of PCF / ECV /ECT by exsufflation time



Scatterplot Matrix of PCF/ECV/ECT by exsufflation time

4.5.2 Correlation between PCF, ETV, ECV (rho)

Preliminary analyses were performed to ensure no violation of the assumptions of normality and linearity. Due to violation of the assumption normal distribution of the PCF values, relationship between PCF, ETV and ECV were investigated using Spearman Rank Order Correlation (rho). There was no correlation between T_e and PCF (rho .039, p>.05): The CI 95% ranged from -.027 to .102, the confidence interval crossed zero and the significance level was higher than 0.05. This means that when increasing the expiration time, the PCF does not increase.

There was a small positive correlation between T_e and ECV (rho .247, p<.05).

There was a medium positive correlation between T_e and ECT (rho .326, p<.05), and between PCF and ECT (rho .326, p<.05). There was a strong positive correlation between PCF and ECV (rho .768, p<.05) and between ECV and ECT (rho .751, p<.05). The correlation between the other variables mean that the confidence interval didn't cross zero and that the significance level was less than 0.05. This means that there are significant positive relationships between T_e and ECV, between T_e and ECT, between PCF and ECT and between PCF and ECV. Increase of T_e increases ECV and ECT.

Table 3. Spearman Rank Order Correlation (rho) between Peak Cough flow, (PCF), Effective cough time (ECT) and Effective cough volume (ECV).

	T_e	PCF	ECV	ECT
T_e	-	.039	.247**	.326**
PCF	.039	-	.768**	.326**
ECV	.247**	.768**	-	.751**
ECT	.326**	.326**	.751**	-

**Correlation is significant at $p<.05$ (2-tailed)

4.6 Hypothesis testing

According to the research questions 6 hypotheses were defined (1.3). Only hypotheses 1- 3 and 6 will be tested here, as the protocol for sampling the VAS scores of self – perceived effect and comfort was found not feasible.

4.6.1 Hypothesis 1: H_0 Longer exsufflation time T_e does not increase PCF.

PCF shows to be insensitive to T_e. With a $p = .23$ and a correlation coefficient of .04 there is no significant relationship between T_e and PCF. Longer exsufflation time T_e does not increase PCF. The null hypothesis cannot be rejected.

4.6.2 Hypothesis 2: H_0 Longer Exsufflation time T_e does not increase ECT.

With a $p = .00$ and a correlation coefficient of .33 there is a significant positive moderate relationship between T_e and ECT. Longer exsufflation time T_e increases ECT. ECT shows to be sensitive to T_e and increases when T_e increases. The null hypothesis can be rejected.

4.6.3 Hypothesis 3: H_o Longer exsufflation time T_e does not increase ECV.

With a $p = .00$ and a correlation coefficient of .24 there is a significant positive weak relationship between T_e and ECV. ECV shows to be sensitive to T_e and increases when T_e increases. Longer exsufflation time T_e does increase ECV. The null hypothesis can be rejected.

4.6.4 Hypothesis 6: H_0 There is no correlation between PCF, ECT, ECV and self – perceived effect and comfort.

Self – perceived effect and comfort is not included in the analysis.

With a $p = .00$ there is a significant relationship between PCF, ECT and ECV. With a correlation coefficient of .77 there is a positive strong correlation between PCF and ECV and means that when PCF increases the ECV increases. With a correlation coefficient of .33 there is positive moderate relationship between PCF and ECT. With a correlation coefficient of .75 there is a positive strong relationship between ECV and ECT.

4.7 Missing data

Because the pneumotachograph had limitation to register flow values above 300 l/min, 310 / 960 cough cycles had the flow value of 300 l/min; 32.3 % of all cough cycles had the PCF of 300 l/min. These values were defined as missing data. Because of the small sample, missing data was given the median PCF value of every time setting (T_e) (Portney, 2020).

5. Discussion

In this chapter, I will after a brief summary of the main findings, discuss methodological aspects and thereafter the results.

5.1 Main findings

In this thesis, the main aim was to test the feasibility of the study design and method, and further to explore alternative outcome measures to assess efficacy of the time settings in MI-E treatment. Overall, we found the study design to be feasible, however we also reviled weaknesses in protocol to record patient reported outcome an in equipment to measure expiratory flow. The protocol and measuring instrument is therefore not feasible in healthy adults.

5.2 Methodological aspects

5.2.1 Design

The present study was a feasibility study aiming to detect weaknesses in study design, this to ensure higher methodological quality for the further study including persons with neuromuscular disorders. A feasibility study also has the purpose to inform a future study and contribute to success (Eldridge, Lancaster, et al., 2016). Our study detected two important weaknesses in the study methods; both a limitation in the pneumotachograph measuring range and an inaccuracy in the questionnaire of self – perceived effect and -comfort. Both important information that must be take into consideration for the further study to ensure higher methodological quality {Eldridge, 2016). The present study also made it possible for us to practice the execution of the intervention, processing of data and calculations of less used ECT and ECV outcome measures. This is important experience to have with us when we examine patients with NMDs, by keeping the examination as smooth and quick as possible. This study had a quantitative design with a focus on the outcome measures (PCF/ECT/ECV), and not on the subjects' experiences, nor the process. A qualitative design would not conduct these findings (Blaxter et al., 2010).

5.2.2 Limitations of the calculations of ECT and ECV

Calculations of ECT and ECV was done by the research physiotherapist, naïve to this kind of data processing and analysis. The processing of data was time consuming, however, the exercises have now been completed and we are better equipped to process and analyze the data from the main study. On the other hand, the research physiotherapist's inexperience may

have led to some errors in the calculations. To strengthen the reliability and validity of these new outcome measures, both a validity study is recommended and automated mathematical algorithms for calculations should be developed.

5.2.3 Measuring instrument

During the analyses, we discovered a roof effect in the PCF values, and especially the PCF values >300 l/min of males were not registered. This was due to the measurement range of the pneumotachograph, and a major limitation in the present study design. Unfortunately, we were not aware of the fact that it does not register the flow values above 300 l/min. The pneumotachograph was not new for our research group. It was used in a previous study measuring PCF in children with NMDs when using MI-E treatment {Hov, 2020 #9}. Here, the PCF values have been well within the range of 300 l/min. However, our future study with adult persons with NMDs will include only patients with already established MI-E treatment in long-term setting. Their spontaneous cough is very weak due to weak respiratory muscles and we do not expect their PCF values to be >300l/min even when using MI-E {Chatwin, 2003 #11}. However, we will perform few measurements with real patients in a clinical context to confirm this hypothesis prior to patient inclusion. Even this roof effect disturbed the results of this feasibility study with healthy volunteers, we believe that the pneumotachograph is clarified as a suitable measuring instrument for future studies with subjects with weak cough. At the same time, we acknowledge it is not an appropriate pneumotachograph in MI-E studies including healthy subjects.

5.2.4 MI-E Intervention

All subjects completed the MI-E intervention according to the test protocol. The study population was healthcare workers at the hospital. Many of them know the technique of MI-E, but some of them were naïve for this treatment. As healthy subject with normal muscle function and normal cough efficiency, the use of MI-E is not necessary and may feel uncomfortable and unnatural. Even if the participants completed the MI-E intervention, some of them expressed it was challenging to relax and let the MI-E device fill their lungs with air. The subjects were instructed to inhale slightly to trigger the insufflation and to cough actively during the exsufflation phase. However, some participants did not find the right rhythm in all the MI-E sequences and this caused asynchrony between the devices MI-E phases and participant effort. Some subjects started to inhale too actively by themselves, and filled their lungs spontaneously before the MI-E device started an insufflation. This can be experienced as an overwhelming feeling of positive pressures to the lungs. These issues might have had an

impact on the effect outcomes that were calculated. Persons using MI-E in long-term setting are is very used to the treatment of MI-E and how it feels. We are of the opinion that these challenges will not be an issue in a future study with individuals with neuromuscular disorders. They have reduced muscle function and will therefore be able to receive the air with less or no muscle resistance and let their lungs be filled with air.

A potential error for the measured effect outcomes is the mask leaks. The high insufflation pressures used can easily cause a leakage between the MI-E facemask and the users face. To avoid this, we asked the study participants to be aware of this and to support the facemask well with their hands to prevent air leakage. Because of this, we could not observe leakage problems at the flow curves and we believe this was not an issue in the present study. This is, however, an important aspect we need to be equipped to cope in the future study including patients. Their arm function is often restricted to control the wheelchair and they have no strength to hold the mask by themselves. Good instructions to the caregivers supporting the facemask during intervention is crucial.

5.2.5 Statistics

Descriptive statistics are used to describe the characteristics of the sample; frequency and percentage, reported as median (min – max) because of the small sample size {Portney, 2020 #63}.

Clustered box plots and histograms were generated to describe the distribution of the variables between men and women. The box in the clustered box plot is the variables interquartile range and contains 50% of the cases. The line across the inside of the box represents the median value. The whiskers protruding from the box go out to the variables smallest and largest value (Portney, 2020 p.320 and 325).

Preliminary analyses were performed to ensure no violation of the assumptions of normality and linearity {Pallant, 2020, p. 137). Due to violation of the assumption of normal distribution of the PCF values, we used the Spearman Rank Order Correlation (*rho*) to investigate the relationship between the outcome measures PCF, ECT, ECV.

5.2.6 Missing data

Missing data were handled with imputation of the median value of the respective time setting. However, this approach results in a larger number of subjects with identical value. This contributes to a reduced variability and biasing results (Portney, 2020).

5.3 Assessment of quality

This study shows a significant relationship between T_e and ECT and ECV and a significant relationship between PCF, ECT and ECV. There are no plausible alternative explanations for the relationships (Portney, 2020). This strengthens the internal validity of this study. However, the reliability of the instrument, the pneumotachograph, compromise the validity of the findings.

Potential new outcome measures were explored and calculation of ECT and ECV was done prior to the intervention. The reliability of these variables therefore compromises the construct validity of this study, the intra-rater reliability and the validity of the measurements. The limitation of the pneumotachograph also affect the validity and the reliability of the measurements, especially in males.

We made an effort strengthening the intra-rater reliability by double blinding the MI-E intervention. Both the research physiotherapist instructing the participants, and the participants were blinded to the T_e used (Portney, 2020).

5.4 Discussion of the results

5.4.1 Sample size

In this present study, the sample size is relatively small, and influences the statistical power. A study with low statistical power may not be able to identify a statistical relationship even if it exists. It might render the study at risk for type-II errors (i.e., failure to detect significant differences that may have been present). Sample size is often the primary limiting factor when a study shows no difference or relationship (Portney, 2020). A small sample size also threatens generalizability of the results, and thus represents a threat to the external validity (Portney, 2020). However, our intention is not to generalize but to explore potential new outcome measures and to provide information to future studies. Additionally, this study was performed in a context of MSc study with limited time. We have performed a power calculation for the future study with persons with NMDs and will include a sufficient number of patients to detect significant differences.

5.4.2 Descriptive statistics

The study sample included healthy adults with a median age in the early forties where 65% was women. By displaying a clustered box plot and histogram of PCF and Exsufflation time we revealed rather low PCF values and a roof effect and we expected higher values in healthy

adults (Chatwin et al., 2003). With this information, we detected the limitation in the pneumotachograph. Nearly 1/3 of cough cycles have the value of 300 l / min, which is the highest value possible to register for this pneumotachograph.

Clustered box plots further reveal outliers and extreme values {Portney, 2020). The number of outliers is the highest in the distribution of PCF values. Due to a small sample size, we chose not to discard the outliers or extreme values. These values may be true values. If more subjects were tested and the pneumotachograph didn't have the limit of 300 l / min, there might be less of a discrepancy between the outliers and the rest of the values (Portney, 2020).

5.4.3 Statistical analyses

In this feasibility study, we found additional analyses not to be applicable because the primary focus is on assessing feasibility to inform the design of the future study and not on determining correlations (Thabane et al., 2016). However, we were to determine feasibility of the outcome measures PCF, ECT, ECV and self-perceived effect and comfort, and had to explore the relationship between T_e and the outcome measures to be able to do that. Due to violation of the assumption of normal distribution of the PCF values, correlations between T_e and PCF / ECT / ECV were assessed by Spearman Rank Order Correlation (rho) {Pallant, 2020).

The analyses show there is no relationship between T_e and PCF and that there is a significant positive relationship between PCF, ECT and ECV. This means that PCF is less sensitive to T_e than ECT and ECV. However, PCF is the usually used outcome measure to predict cough efficacy (Morrow et al., 2013). Correlation analyses show a significant positive relationship between all three outcome measures; PCF, ECT and ECV. A positive correlation means that increase in one of the variables cause an increase in the others. It is therefore a possibility that with a more suitable measuring instrument and a larger sample, a relationship between T_e and PCF might be found.

There were 20 subjects in the sample and they provided us each with 6 cough cycles per time setting T_e. That means 48 cough cycles per subject. All together we analyzed 960 cough cycles. However, these values are not 960 independent values from 960 different subjects and we need to take the degree of dependency in the data into account, when interpreting the results. This may threaten the generalizability of the results {Portney, 2020 #63}

5.5 Hypotheses

5.5.1 Hypothesis 1: H_0 Longer exsufflation time T_e does not increase PCF.

PCF shows to be insensitive to T_e. Longer exsufflation time T_e does not increase PCF. Although the rejection of the hypothesis is based on the result of objective statistical procedure, we are not guaranteed to make a correct decision. There is a possibility that we are making a Type II error (Portney, 2020) by not rejecting the hypothesis; there is a possibility, with a larger sample and with a more suitable measuring instrument, we could have the power to show that there is a relationship between T_e and PCF. This would need to be further investigated in a future study with a larger sample.

5.5.2 Hypothesis 2: H_0 Longer Exsufflation time T_e does not increase ECT.

ECT shows to be sensitive to T_e. In the study of Lacombe and co-workers (2014) they tested patients with NMDs and they found a relationship between the duration of the positive pressure and ECT (Lacombe et al., 2014). We can confirm this relationship in our study with healthy adults; longer exsufflation time T_e increases ECT. This indicate that longer exsufflation time give more time spent above 180 l / min. This is useful information in MI-E treatment because the treatment should be as effective as possible. Knowing when the "window" for mobilizing secretion is at its optimal, may contribute to a more targeted treatment.

5.5.3 Hypothesis 3: H_o Longer exsufflation time T_e does not increase ECV.

ECV shows to be sensitive to T_e. In the study of Lacombe et al. (2019), they found that ECV was more sensitive to upper airway collapse than PCF (Lacombe et al., 2019). With an insufflation/exsufflation time at 2.5 sec and a gradually titrated insufflation/exsufflation pressure, PCF consistently increased with decreasing the exsufflation pressure, regardless collapse of upper airway collapse or not. PCF was always highest at the lowest exsufflation pressure. However, the ECV stopped increasing when collapse of the airway occurred (Lacombe et al., 2019). With a sample of 27 patients 22 patients experienced upper airway collapse with an exsufflation pressure at > -50 cmH_2O. 5/27 experienced upper airway collapse from the beginning of the titrating at 20 cmH_2O (Lacombe et al., 2019).

In our study ECV shows to be sensitive to T_e and increases when T_e increases. To ensure the MI-E treatment to be as effective as possible it is useful information to know which time setting T_e provides PCF above 180 l / min. Knowing how much volume above 180 l / min at T_e may be a very useful indicator of how effective the MI-E treatment is. Further, airway collapse may be missed if only peak expiratory flow or PCF is measured, because these

parameters may be paradoxically increased in the mouth when the collapse causes rapid expulsion of the air contained in the upper airway {Lacombe, 2019 #7}. In this present study the pressure settings were 40/-40 cmH_2O and the insufflation time was set to 2.5 sec. We wanted to explore what impact exsufflation time has on the efficacy of MI-E treatment and results in this study shows a significant relationship between T_e and ECV and a trend of longer T_e gives a higher ECV in the male distribution. However, this needs to be further investigated in future studies.

5.5.4 Hypothesis 6: H_0 There is no correlation between PCF, ECT, ECV and self – perceived effect and comfort.

Self – perceived effect and comfort is not included in the analysis as we detected weaknesses in the protocol. Because of the design error of the questionnaire of self – perceived effect and comfort the VAS was not able to capture the score of every cough cycle. The protocol is therefore not feasible in healthy adults.

There is a significant relationship between PCF, ECT and ECV. It means that when one of the variables increase, we can expect an increase of the other variables. The three variables will describe efficacy with different perspectives and supplement each other and give a more nuanced understanding of when the mobilization of secretion is the most effective during MI-E treatment. Furthermore, a parameter of detecting upper airway collapse is crucial to be able to individualize and optimize the MI-E treatment.

The fact that there is a relationship between these variables indicate that ECT and ECV can function as outcome measures for evaluation the efficacy of MI-E treatment, ensuring that the aspect of time and volume is included in the evaluation of efficacy.

5.6 Feasibility

In this study, Effective Cough Time (ECT) Effective Cough Volume (ECV) was more sensitive to T_e than PCF was. That may indicate that ECT and ECV can give us valuable information of the time window during T_e that PCF is at a certain level to mobilize secretion; *when* is the magic window to mobilize secretion?

Peak Cough Flow (PCF) is the most common outcome measure to assess cough efficiency and effect of MI-E treatment, but only provides us with a peak value of the expiratory flow {Chatwin, 2003), {Lachal, 2019). We suggest that ECT and ECV in addition to PCF can give

us a more nuanced understanding of the efficacy of MI-E treatment, and help us to individualize the treatment better.
However, we detected the limitation of pneumotachograph and we need to take this into account when evaluating the different outcome measures. To be able to come closer to a conclusion, we need to verify our findings and to investigate the sensitivity for T_e in PCF further in a study with individuals with neuromuscular disorders.

This study shows that ECT and ECV are feasible outcome measures in healthy adults and the PCF is less feasible. However, this must be further investigated and the violations of the assumptions for the statistical analysis must be taken into account when evaluating the results.

However, the measuring instrument and the questionnaire of evaluation self – perceived effect and comfort show not to be feasible in healthy adults. A more suitable pneumotachograph is recommended in a study with healthy adults.

5.7 Clinical value and future prospects

Knowledge about MI-E settings is beneficial both for health professionals working with patients with respiratory problems and for the patient population. To perform MI-E treatment several times a day may be demanding of resources and tiring for the patients. It is thus important that the treatment is as accurate, efficient and gentle as possible. The results of this study are not generalizable to individuals with neuromuscular disorders, however, the results may challenge the theory we base our clinical practice on and make foundation for a later study to test the findings on individuals with NMD and further research in the field.

There are only two articles where ECT and ECV are defined (Lacombe et al., 2014), (Lacombe et al., 2019). However, knowledge of normal ECV and ECT values does not exist. In this present study, we obtained new knowledge of these two novel outcome measures and we did actually report the normal values in healthy individuals. This information contributes with important knowledge in further investigation of the ECT and ECV, in a future study with neuromuscular individuals. Further, this knowledge may, in the future, also contribute to modify todays clinical practice in respiratory physiotherapy, in MI-E treatment of neuromuscular individuals.

6. Conclusion

This study systematically investigated the impact exsufflation time has on the efficacy of MI-E treatment in healthy adults.

This protocol is not feasible in healthy adult and needs to be rectified for future studies. The measuring instrument shows not to be feasible in healthy adults, however, it is suitable in studies with NMDs.

PCF shows to be less sensitive to the exsufflation time than ECT and ECV and the study shows a significant relationship between PCF, ECT and ECV. Time settings should be investigated further. This to be able to individualize the MI-E treatment and increase the efficacy.

These results show the potential of ECT and ECV as new outcome measures of efficacy. They may contribute to a more nuanced understanding of the efficacy of MI-E treatment and supply PCF with information of time, volume and airway collapse.

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Attachment 1.

The Cough Assist E70 settings

Settings (Unit)	Available options	Settings used	Comments
Mode	Auto/Manual	Auto	
Cough-Trak	On/Off	Off	Lung model set up as passive simulating lacking effort from respiratory muscles, thus triggering of cough not possible.
Inhale Pressure (cmH_2O)	0 to 70	15 to 50	Increments of 5 cmH_2O used
Inhale Flow (l/min)	Low/Medium/High	Medium	i.g. rise time. The CA E70 does not control flow but only pressure, thus he inhale flow is determined by the mechanics of the patient airway and the difference of the insufflation and exsufflation pressure in use.
Inhale time (seconds)	0 to 5	0 to 2	Increments of 0.5 sec used.
Pause time (seconds)	0 to 5	0.5	
Exhale pressure (cmH_2O)	0 to -70	-20 to -50	Increments of -10 cmH_2O used.
Exhale time (seconds)	0 to 5	0 to 1	0.5 and 1.0 seconds tested.
Oscillation	(On/Off)	Turned off	

Attachment 2:

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst C	Anders Strand		24.11.2020	182325
			Deres referanse:	

Tiina Maarit Andersen

Hvordan påvirker ekspirasjonstiden effekten av hostemaskin for voksne med

NMD?

Forskningsansvarlig: Helse Bergen HF - Haukeland universitetssykehus

Søker: Tiina Maarit Andersen

Søkers beskrivelse av formål:

Denne studien skal utvikle kunnskap som skal underbygge og modifisere gjeldende klinisk lungefysioterapipraksis for personer med nevromuskulære sykdommer. Nevromuskulære sykdommer fører til muskelsvekkelse i kroppens muskler, der også puste- og hostemusklene kan bli rammet. I slike tilfeller blir respirasjonen påvirket og langtids mekanisk ventilasjon (LTMV) brukes til å kompensere pasientens sviktende ventilasjon og hostemaskin brukes til å forebygge og behandle luftveisinfeksjoner. I dette prosjektet har vi til hensikt å optimalisere den kliniske behandlingen med hostemaskinen ved å undersøke systematisk hvilke tidsinnstillinger på ekspirasjonstiden som er de mest effektive. I tillegg skal prosjektet sammenligne flere nye utfallsmål for effekt med det etablerte utfallsmålet. Studiedeltagerne vil bli rekruttert fra Nasjonalt register for langtids mekanisk ventilasjon (LTMV) etter følgende inklusjonskriterier: voksne personer med arvelige nevromuskulære sykdommer som bruker puste- og hostehjelpemidler hjemme, og som går til regelmessige kontroller ved Haukeland universitetssykehus, Oslo Universitetssykehus eller Akerhus Universitetssykehus for sin pustesvikt. Pasienter med diagnosen Amyotrofisk Lateral

Sklerose (ALS) eller pustestøtte via trakeostomi vil bli eksludert. Det forventes å inkludere 43 pasienter til studien. Pasientene vil få tilsendt skriftlig informasjon om studien samt samtykkeskjema. Forskningsfysioterapeut vil kontakte de som har fått tilsendt informasjon for å å høre om det er ønskelig å delta i studien. Det er helt frivillig å delta i studien, men studien forutsetter signert samtykke, som leveres når deltageren kommer til undersøkelse.

Datainnsamlingen vil foregå vil foregå på Nevrologisk poliklinikk, Enhet for arvelige nevromuskulære tilstander (EMAN) ved Oslo Universitetssykehus (OUS), på

Lungepoliklinikken ved Haukeland universitetssjukehus (HUS) og på lungepoliklinikken ved Akershus universitetssykehus (AHUS). Undersøkelsen kan også gjennomføres hjemme hos pasienten dersom det er vanskelig for pasienten å komme til sykehuset.

Ved oppstart vil forskningsfysioterapeuten registrere kjønn, alder, vekt, diagnose, om pasienten har PEG-sonde, svelgevansker eller er scolioseoperert, hvor lenge pasienten har brukt hostemaskin hjemme og hvor ofte pasienten bruker hostemaskinen. Vi vil også gjøre lungefunksjonsmålinger og laste ned bruksdata fra hostemaskinen som pasienten bruker hjemme.

I selve undersøkelsen vil det bli brukt hostemaskin type Cough Assist E70, Philips Respironics. Innstillinger vil være samme for alle deltagere, hvor ekspirasjonstiden vil bli endret i randomisert rekkefølge. En pneumotachograph vil registrere luftstrømmen under testprosedyren. Både topp luftstrømshastighet (peak cough flow), samt tiden og ekspirasjonsvolumet ved PCF over 160 l/min regnes ut.

Pasientene vil gjennomgå 6 hostesykluser for hver innstilling. Det vil være minst 30 sek pause mellom hver innstilling for å unngå hyperventilering. Etter hver syklus vil forskningsfysioterapeut spørre pasienten om den selvopplevde effekten og komforten ved MI-E ved å benytte Visuell Analog Skala (VAS). Vi vil undersøke i analysene om ekspirasjonstid påvirker til effekt av hostemaskinen og om det er sammenheng mellom utfallsparametere.

Resultatene vil bli formidlet som en vitenskapelig artikkel. Etter datainnsamlingen er avsluttet og analysene er gjennomført, deltagerne vil få en skriftlig oppsummering av sine egne testresultater, samt en generell oppsummering av studiets resultater.

REKs vurdering

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst C) i møtet 29.10.2020. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Formålet med gjennomføringen av studien er å utvikle kunnskap som skal underbygge og modifisere gjeldende klinisk lungefysioterapipraksis for personer med nevromuskulære sykdommer. En skal systematisk undersøke hvilke tidsinnstillinger på ekspirasjonstiden som er de mest effektive med den hensikt å optimalisere den kliniske behandlingen med hostemaskin. I tillegg skal flere nye utfallsmål for effekt sammenligne med det etablerte utfallsmålet.

Komiteen har ingen forskningsetiske innvendinger til gjennomføring av forskningsprosjektet.

Vedtak

Godkjent

Komiteen har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes som omsøkt, med hjemmel i helseforskningsloven § 10.

Komiteen gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 30.09.2025. Av dokumentasjons- og oppfølgingshensyn skal opplysningene likevel bevares inntil 30.06.2030. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Med vennlig hilsen,

Britt-Ingjerd Nesheim

Prof. Dr.med

Komiteleder, REK sør-øst C

Øyvind Grønlie Olsen

Seniorrådgiver REK sør-øst

Dokumentet er elektronisk signert

Kopi av vedtak: Forskningsansvarlig institusjon.

Sluttmelding

Søker skal sende sluttmelding til REK sør-øst C på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12. Dersom prosjektet ikke igangsettes eller gjennomføres skal prosjektleder også sende melding om dette via sluttmeldingsskjemaet.

Søknad om å foreta vesentlige endringer

Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

Attachment 3.

Region:	Saksbehandler:		Vår dato:	Vår referanse:
REK sør-øst C	Anders Strand	Telefon:	01.07.2021	182325

Tiina Maarit Andersen

Prosjektsøknad: Hvordan påvirker ekspirasjonstiden effekten av hostemaskin for voksne med NMD?

Søknadsnummer: 182325

Forskningsansvarlig institusjon: Helse Bergen HF - Haukeland universitetssykehus
Samarbeidende forskningsansvarlige institusjoner: Oslo universitetssykehus HF, Helse Bergen HF - Haukeland universitetssykehus, Akershus universitetssykehus HF

Prosjektsøknad: Endring godkjennes med vilkår.

Søkers beskrivelse

Denne studien skal utvikle kunnskap som skal underbygge og modifisere gjeldende klinisk lungefysioterapipraksis for personer med nevromuskulære sykdommer. Nevromuskulære sykdommer fører til muskelsvekkelse i kroppens muskler, der også puste- og hostemusklene kan bli rammet. I slike tilfeller blir respirasjonen påvirket og langtids mekanisk ventilasjon (LTMV) brukes til å kompensere pasientens sviktende ventilasjon og hostemaskin brukes til å forebygge og behandle luftveisinfeksjoner. I dette prosjektet har vi til hensikt å optimalisere den kliniske behandlingen med hostemaskinen ved å undersøke systematisk hvilke tidsinnstillinger på ekspirasjonstiden som er de mest effektive. I tillegg skal prosjektet sammenligne flere nye utfallsmål for effekt med det etablerte utfallsmålet. Studiedeltagerne vil bli rekruttert fra Nasjonalt register for langtids mekanisk ventilasjon (LTMV) etter følgende inklusjonskriterier: voksne personer med arvelige nevromuskulære sykdommer som bruker puste- og hostehjelpemidler hjemme, og som går til regelmessige kontroller ved Haukeland universitetssykehus, Oslo Universitetssykehus eller Akerhus Universitetssykehus for sin pustesvikt. Pasienter med diagnosen Amyotrofisk Lateral
Sklerose (ALS) eller pustestøtte via trakeostomi vil bli eksludert. Det forventes å inkludere 43 pasienter til studien. Pasientene vil få tilsendt skriftlig informasjon om studien samt samtykkeskjema. Forskningsfysioterapeut vil kontakte de som har fått tilsendt informasjon for å å høre om det er ønskelig å delta i studien. Det er helt frivillig å delta i studien, men studien forutsetter signert samtykke, som leveres når deltageren kommer til undersøkelse. Datainnsamlingen vil foregå vil foregå på Nevrologisk poliklinikk, Enhet for arvelige nevromuskulære tilstander (EMAN) ved Oslo Universitetssykehus (OUS), på

Lungepoliklinikken ved Haukeland universitetssjukehus (HUS) og på lungepoliklinikken ved Akershus universitetssykehus (AHUS). Undersøkelsen kan også gjennomføres hjemme hos pasienten dersom det er vanskelig for pasienten å komme til sykehuset.
Ved oppstart vil forskningsfysioterapeuten registrere kjønn, alder, vekt, diagnose, om pasienten har PEG-sonde, svelgevansker eller er scolioseoperert, hvor lenge pasienten har brukt hostemaskin hjemme og hvor ofte pasienten bruker hostemaskinen. Vi vil også gjøre lungefunksjonsmålinger og laste ned bruksdata fra hostemaskinen som pasienten bruker hjemme.
I selve undersøkelsen vil det bli brukt hostemaskin type Cough Assist E70, Philips Respironics. Innstillinger vil være samme for alle deltagere, hvor ekspirasjonstiden vil bli endret i randomisert rekkefølge. En pneumotachograph vil registrere luftstrømmen under testprosedyren. Både topp luftstrømshastighet (peak cough flow), samt tiden og ekspirasjonsvolumet ved PCF over 160 l/min regnes ut.
Pasientene vil gjennomgå 6 hostesykluser for hver innstilling. Det vil være minst 30 sek pause mellom hver innstilling for å unngå hyperventilering. Etter hver syklus vil forskningsfysioterapeut spørre pasienten om den selvopplevde effekten og komforten ved MI-E ved å benytte Visuell Analog Skala (VAS). Vi vil undersøke i analysene om ekspirasjonstid påvirker til effekt av hostemaskinen og om det er sammenheng mellom utfallsparametere. Resultatene vil bli formidlet som en vitenskapelig artikkel. Etter datainnsamlingen er avsluttet og analysene er gjennomført, deltagerne vil få en skriftlig oppsummering av sine egne testresultater, samt en generell oppsummering av studiets resultater.

REK viser til endringssøknad mottatt 01.06.2021, for prosjekt «Hvordan påvirker ekspirasjonstiden effekten av hostemaskin for voksne med NMD?». Komiteleder for REK sør-øst C har vurdert søknaden på fullmakt fra REK sør-øst C, med hjemmel i helseforskningsloven §11.

Vedlagt endringssøknaden lå revidert protokoll (datert 01.06.21) samt informert samtykke for friske kontroller.

Den omsøkte endringen består i å inkludere et pilotprosjekt, ettersom Covid-19 pandemien har vanskeliggjort gjennomføringen av prosjektet. Pilotundersøkelsen skal utføres på 10-20 friske helsearbeidere over 18 år, som er alder- og kjønnsmatchet med studiepopulasjonen. Alle skal signere samtykke, og det nye utarbeidede informasjonsskrivet lå vedlagt endringssøknaden. Målet med pilotprosjektet er å sikre god metode slik at testprosedyren vil bli gjennomført på en mer skånsom måte, og at det vil oppleves som mindre påkjennende for pasientene.

REKs vurdering

Komiteens leder har vurdert den omsøkte endringen, og har to innvendinger:

1. Det er uklart hva selve prosedyren går ut på. REK forstår det slik at maskinen igangsetter hoste for personene som benytter den. Hva som skal skje og hvordan bør komme bedre frem i informasjonsskrivet, og det bør også beskrives hva slags ubehag deltakerne kan forvente i løpet av undersøkelsen.
2. Det settes som vilkår at det ikke skal rekrutteres medarbeidere som står så nær rekrutteringsansvarlige at det kan oppfattes som press til å delta.

Det settes derfor som vilkår at informasjonsskrivet skal oppdateres i henhold til punkt 1, og at rekrutteringsprosedyren klargjøres i henhold til punkt 2. Informasjonsskriv og protokoll må revideres i henhold til REKs kommentarer, og dokumentene med sporede endringer skal sendes REK til orientering via skjemaet "endring og/eller henvendelse" i REK-portalen.

Vedtak

REK har gjort en forskningsetisk vurdering av endringene i prosjektet, og godkjenner prosjektet slik det nå foreligger, jf. helseforskningsloven § 11, under forutsetning av at ovennevnte vilkår oppfylles.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

Vennligst oppgi vårt referansenummer i korrespondanse.

Sluttmelding

Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest senest 6 måneder etter sluttdato 30.09.2025, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring

Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang

Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar av dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen,

Britt Ingjerd Nesheim
Prof. Dr.med
Komiteleder, REK sør-øst C

Marianne Bjørnerem Rådgiver,
REK sør-øst

Kopi til:

Helse Bergen HF - Haukeland universitetssykehus
Oslo universitetssykehus HF, Helse Bergen HF - Haukeland universitetssykehus, Akershus universitetssykehus HF Brit Hov, Gry Cecilie Dalby

Attachment 4.

VIL DU DELTA I FORSKNINGSPROSJEKTET

«HVORDAN PÅVIRKER UTPUSTTIDEN EFFEKTEN AV HOSTEMASKIN FOR VOKSNE MED NEVROMUSKULÆRE SYKDOMMER?»

FORMÅLET MED PROSJEKTET OG HVORFOR DU BLIR SPURT

Dette er et spørsmål til deg om å delta i et forskningsprosjekt som **frisk kontroll**.

Formålet med prosjektet er å få kunnskap om mer effektive hostemaskininnstillinger hos personer med nevromuskulære sykdommer. Hostemaskin er et hjelpemiddel for å få opp slim fra luftveiene. Den fungerer på den måten at luft først blåses inn i lungene og deretter suges ut sammen med slim fra de sentrale luftveiene. Det er mye som tyder på at hostemaskinens innstillinger påvirker effekten av behandlingen og at behandlingstrykket er en viktig faktor. Vi tror også at tidsinnstillingene for utpustfasen har betydning, men dette er ikke tidligere undersøkt.

Det er heller ikke kartlagt hva normalverdiene for effekt av hostemaskin er hos friske voksne. En kontrollgruppe vil være referanse til sammenlikning med hovedgruppen og bidra til enda større og mer nyansert forståelse av effekten av hostemaskin hos voksne med nevromuskulære sykdommer.

Målet med denne studien er å etablere kunnskap om tidsinnstillinger for selve utpustfasen med hostemaskin. Dette kan øke behandlingseffektiviteten til personer med nevromuskulær sykdom som har svak hosteevne. Det kan videre optimalisere behandlingen og dermed forebygge og behandle eventuelle lungeinfeksjoner bedre og dessuten forhindre sykehusinnleggelser. Vi ønsker å lære av våre erfaringer slik at de kan bli til nytte også for andre pasientgrupper med tilsvarende svak hosteevne. Derfor utføres undersøkelsene systematisk og innenfor rammene av en forskningsstudie.

Prosjektet er et samarbeidsprosjekt mellom Nasjonalt Kompetansetjeneste for Hjemmerespiratorbehandling og Nasjonalt register for langtids mekanisk ventilasjon, Lungeavdelingen på Haukeland Universitetssykehus (HUS) i Bergen, Enhet for medfødte og arvelige nevromuskulære tilstander (EMAN) ved Oslo Universitetssykehus (OUS), Lungeavdelingen på Akershus Universitetssykehus (AHUS) og Universitet i Oslo (UiO).

HVA INNEBÆRER PROSJEKTET FOR DEG?

Deltakelsen innebærer at du kommer til Lungepoliklinkken ved Haukeland Universitetssykehus (HUS) og gjennomgår testprosedyren.

Først vil vi registrere bakgrunnsinformasjon (navn, fødselsdato, kjønn, vekt, høyde). Videre vil det bli utført lungefunksjonsmålinger sittende med elektroniske spirometriapparater. Lungefunksjonsmålingene skal måle luftvolum, luftstrøm og lufttrykk. Deretter utfører vi selve undersøkelsen med hostemaskinen. Hele prosedyren vil bli forklart til deg i forkant av undersøkelsen og om du ønsker vil du få mulighet til å teste hostemaskinen før undersøkelsen, slik at du er forberedt på hvordan det vil oppleves og vende deg litt til det.

Under undersøkelsen skal du sitte oppreist på en stol og du vil bli koblet til hostemaskinen med en maske som sitter over nesen og munnen. På masken er det koblet til en luftstrømsmåler, et filter og en slange som videre er koblet til hostemaskinen. Hostemaskinen er under undersøkelsen innstilt med standardinnstillinger bortsett fra utpusttiden som endres underveis. Vi vil bruke 8 forskjellige utpusttider og de vil komme i tilfeldig rekkefølge. Hverken du eller forskningsfysioterapeuten vil vite hvilken rekkefølge utpusttidene vil komme i. Vi skal bruke følgende utpusttider i tilfeldig rekkefølge: 0.5 sek, 1.0 sek, 1.5 sek, 2.0 sek, 2.5 sek, 3.0 sek, 3.5 sek og 4.0 sek. Du vil gjennomgå 6 hostesykluser ved hver tidsinnstilling. Etter hver hostesyklus får du 60 sek pause før vi forandrer utpusttiden før neste hostesyklus. Ved innpust vil du oppleve at det kommer luft fra hostemaskinen og inn i masken som du har over nese og munn. Du vil oppleve at luften blåser opp lungene dine og dette kan oppleves som noe ubehagelig når man ikke bruker hostemaskin til vanlig. Denne luften kommer med et visst trykk i 2.5 sekunder før maskinen slår om til utpust. Da vil du oppleve et sug i masken som også er med et gitt trykk og med 8 forskjellige utpusttider i tilfeldig rekkefølge. Etter hver hostesyklus vil vi be deg om å angi, på en skala fra 0 til 10, din selvopplevde effekt og komfort ved hostemaskinbehandlingen.

En luftstrømsmåler vil være koblet inn mellom maske og slangesettet til hostemaskinen. Dette registrerer luftstrøm, luftvolum og trykk under hele undersøkelsen.

Undersøkelsen vil bli gjennomført av forskningsfysioterapeut. Hele undersøkelsen, fra du kommer til du er helt ferdig, tar cirka en time.

MULIGE FORDELER OG ULEMPER

Deltakelsen innebærer at du må komme innom Lungepoliklinkken ved Haukeland Universitetssykehus og bruke 1 time av din arbeidsdag / fritid til å gjennomgå testingen.

Du vil bidra til økt kunnskap om normalverdier for effekt av hostemaskin hos friske voksne som igjen bidrar til enda bedre og nyansert forståelse av effekten av hostemaskin hos voksne med nevromuskulære tilstander. Du vil også bidra til å sikre god metode ved gjennomføring av hovedprosjektet, som kommer pasienten til gode.

Retningslinjene for gjennomføring av undersøkelsen vil til enhver tid følge oppdaterte nasjonale og lokale retningslinjer fra Folkehelseinstituttet (FHI) og Haukeland Universitetssjukehus (HUS). Alle deltakere vil bli screenet for Covid-19 symptomer før testing. Testingen vil **ikke** bli utført hvis det blir rapportert om positiv Covid – 19 -test eller om symptomer på Covid-19-infeksjon: nye symptomer i øvre luftveier eller feber. Vi vil overholde anbefalt avstand under de delene av datainnsamlingen hvor det er mulig. Under undersøkelsen benytter forskerne smittevernsutstyr som vernebriller/visir, hansker og munnbind.

Vi vil bytte bakteriefilter på hostemaskinen mellom hver deltaker samt desinfisere alle overflater nøye. Vi vil dessuten ha et ekstra bakteriefilter i kretsen for å beskytte både deg og utstyret.

Som frisk har du god puste- og hostekraft og har derfor ikke behov for hostemaskin. Hostemaskin vil derfor kunne oppleves som unaturlig og ubehagelig, men dette bedres ofte utover i undersøkelsen.

Ved å gjennomgå denne undersøkelsen med hostemaskin vil du oppnå større forståelse for hvordan det føles å bruke hostemaskin, og det kan være en fordel i ditt pasientarbeid.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE DITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dersom du trekker tilbake samtykket, vil det ikke forskes videre på dine helseopplysninger. Du kan også kreve at dine helseopplysninger i prosjektet slettes eller utleveres innen 30 dager. Adgangen til å kreve sletting eller utlevering gjelder ikke dersom materialet eller opplysningene er anonymisert. Denne adgangen kan også begrenses dersom opplysningene er inngått i utførte analyser.

Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte prosjektleder (se kontaktinformasjon på siste side).

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet under formålet med prosjektet, og planlegges brukt til 2026. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra

REK og andre relevante myndigheter. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Du kan klage på behandlingen av dine opplysninger til institusjonen sitt personvernombud.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger (=kodede opplysninger). En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun prosjektleder Tiina Andersen og forskningsfysioterapeut Gry Cecilie Dalby som har tilgang til denne listen.

Opplysningene om deg vil bli oppbevart i fem år etter prosjektslutt av kontrollhensyn.

FORSIKRING

Ved eventuell skade gjelder pasientskadeloven.

GODKJENNINGER

Regional komité for medisinsk og helsefaglig forskningsetikk har gjort en forskningsetisk vurdering og godkjent prosjektet, saksnr. 182325.

Oslo Universitetssykehus / Haukeland Universitetssjukehus og prosjektleder Tiina Andersen og forskningsfysioterapeut Gry Cecilie Dalby, er ansvarlig for personvernet i prosjektet.

Vi behandler opplysningene basert på ditt samtykke.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet eller ønsker å trekke deg fra deltakelse, kan du kontakte forskningsfysioterapeut Gry Cecilie Dalby: uxdagr@ous-hf.no / mobil 41410034 eller prosjektleder Tiina Andersen: tiina.andersen@helse-bergen.no / mobil 95890460.

Dersom du har spørsmål om personvernet i prosjektet, kan du kontakte personvernombudet ved institusjonen: personvernombudet@helse-bergen.no

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER OG TESTRESULTATER BRUKES SLIK DET ER BESKREVET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Sted og dato

Signatur

Rolle i prosjektet