Upper Airway Assessment and Responses during Mechanically Assisted Cough - A Narrative Review

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Title page

1. TITLE OF THE ARTICLE

Upper Airway Assessment and Responses during Mechanically Assisted Cough - A Narrative Review

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When ability to cough is impaired, secretion clearance may be assisted and augmented by Mechanical Insufflation-Exsufflation (MI-E). In some individuals, the efficacy of MI-E may be hampered by counterproductive upper airway reactions, where the airways close in response to positive pressures. In order to fully utilize the therapeutic potential inherent in the MI-E technology, we need a better understanding of the pathophysiology behind these untoward reactions. There is an increasing interest in monitoring and measuring upper airway responses to MI-E, and how such information can be used to optimize the MI-E settings. The purpose of this narrative review is to increase the theoretical understanding of larynx as a respiratory organ, summarize the current literature in the area, and provide insight into how this knowledge can affect current clinical practice.

KEY WORDS

Mechanical insufflation–exsufflation, cough augmentation, upper airways, larynx, laryngoscopy, assessment, neuromuscular disease, motor neuron disease, bulbar paresis
INTRODUCTION

Clearing the airways for secretions is vital to sustain a healthy respiratory system. The process entails shearing of the secretions from the airway walls and then propelling the debris towards the larger airways. Secretion relocation depends on airflow velocity as well as the shape and cross-sectional area of the airway.\(^\text{1,2}\) Cough is the final part of airway secretion clearance, and the mechanism by which the central airways are cleared.\(^\text{1}\)

Neuromuscular disorders (NMDs) may cause muscular weakness leading to weak cough and inability to clear the airways sufficiently, accumulation of secretion and complications like dyspnea and pneumonia. Mechanical Insufflation-Exsufflation (MI-E) is used to assist cough in persons with NMD. The device simulates normal cough by 1) applying a positive pressure leading to insufflation and lung expansion followed by 2) a rapid switch to a negative pressure leading to an exsufflation sucking air and consequently secretions out of the airways. MI-E is considered safe and effective\(^\text{3-10}\) and may in conjunction with non-invasive ventilation (NIV) delay or prevent intubation or tracheostomy.\(^\text{11-13}\) Based on successful experiences in individuals with NMD, MI-E treatment has been applied also in subjects with impaired cough for other reasons, such as in critically ill individuals under intensive care,\(^\text{14-16}\) and in persons with other neurologic disorders like cerebral palsy,\(^\text{17-20}\) neuropathy, multiple sclerosis, parkinson,\(^\text{19}\) myotonic dystrophy\(^\text{19,21}\) and Kennedy’s disease.\(^\text{22}\)

MI-E therapy applied non-invasively (via a face-mask) does not succeed in all. Challenging individuals often display one common denominator, namely disturbed laryngeal function or/and bulbar symptoms. Particularly in individuals with bulbar muscular dysfunction, such as Amyotrophic Lateral Sclerosis (ALS), the non-invasive use of MI-E has proven difficult, as poor laryngeal control seemingly obstruct the airflow in some.\(^\text{23-29}\) These observations have changed the current landscape of MI-E research. Understanding of the upper airway function, and especially the complexity of larynx as an organ, is necessary to make a difference.
Numerous groups now engage in projects aiming to monitor and prevent counterproductive upper airway responses, increasing the knowledge on optimal adjustments of the MI-E settings.

We searched for literature on assessment and interpretation of upper airways responses to MI-E. The purpose of this narrative review is to increase the theoretical understanding of larynx as a respiratory organ, to summarize the literature on methods used to assess the upper airways during MI-E and the response patterns that have been described, and to provide insight into how this understanding may affect current practice.

THEORETICAL BACKGROUND

The laryngeal role in the healthy

The constitution of the upper airways is easy to understand from an evolutionary point of view. The human evolution from water to dry land existence altered the pulmonary development by allowing gas exchange directly from the air. The lungs became integrated within the thoracic cage, including a complex “gateway function” centrally positioned in the upper airways, guarding the entrance to the lower airways and protecting the delicate distal gas exchange surfaces from foreign bodies, injury and dehydration. Whereas the laryngeal function in primitive species is primarily protective, development of the human larynx led to an abduction mechanism better facilitating ventilation. Further, a demand for phonation required the gateway to be able to perform fine-tuned rapid movements of narrowing and opening and thus, the laryngeal inlet became a potential major point of airflow resistance within the respiratory tract. This gives an upper airway that crosses the upper gastrointestinal tract, with the larynx centrally positioned in an intersection that must intergrate both the primitive protective laryngeal function, continuous need for ventilation, transmission of high volume ventilation during exercise, phonation, swallowing and cough.
The larynx consists of the hypopharyngeal, supraglottic, glottic and subglottic areas (Figure 1), and entails airway mucosa, rigid cartilage skeletons, ligaments and muscles for adduction and abduction. These structures together create a dynamic cavity with movements at several levels. Laryngeal muscles are under voluntary as well as reflex control, controlled by sensory-motor reflex responses involving glossopharyngeal, pharyngeal, laryngeal and tracheobronchial sensory receptors. The larynx senses gases, liquids and solids, and it is one of the most highly innervated organs in humans. Innervation is by the internal branch of the superior laryngeal nerve and the recurrent laryngeal nerves; both branches of the vagal nerve. Extrinsic muscles move the larynx as a whole. Intrinsic muscles serve as abductors and stabilizers, all act more or less directly on the true vocal folds.

The larynx accounts for approximately 25% of total resistance during mouth breathing at a resting airflow of about one liter per second. The effort to overcome this resistance requires 12-30% of the total respiratory work. At quiet breathing, glottic abduction (opening) is fundamental for free airflow in and out of the lungs at the least possible resistance. The glottis widens during inspiration and narrows slightly during expiration. Forced inspiration and expiration, including cough, leads to increased activation of small intrinsic laryngeal muscles. In light of the importance of laryngeal abduction for proper airflow, it is somewhat unexpected that the larynx has several adductor muscles, but only one abductor muscle. Musculus Cricoarytenoideus Posterior (PCA) operates in a phasic relationship with the diaphragm, where diaphragmatic vagal stimulation occurs synchronized with increased PCA activity, leading to laryngeal abduction (opening) immediately before diaphragmatic contraction. The equilibrium of forces between the abductor and adductor muscles determines the size of the laryngeal inlet. This balance can be disturbed by weakness of the abductor muscle or increased activity of the adductor muscles, or vice versa.
Rapid occlusion to prevent foreign bodies entering the airways is a vital responsibility of the larynx, and it has been proposed that adductive movements by nature are dominant to abductive. Two mechanisms prevent aspiration; reflexive laryngeal closure and a rapid expulsion of inhaled material, usually presenting simultaneously and synchronized. Stimulation of extremely sensitive supraglottic receptors normally induces complex adductor reflexes that prevent aspiration. In fact, otolaryngologists use positive air pressure stimulation to provoke laryngeal reflex activities, such as laryngeal closure and swallowing. Positive air pressure applied to the laryngeal vestibular mucosa activates nerve afferents in the internal branch of the superior laryngeal nerve, releasing the laryngeal closure reflex. Positive air pressure to the anterior facial area in the oral cavity activates glossopharyngeal afferents and elicit swallowing.

**Cough is not a cough without a functioning larynx**

Normal cough proceeds in three phases. First, the inspiratory muscles create a negative intrathoracic pressure that leads to air flowing through the upper airways to the lungs that become inflated (deep inspiration phase). Second, the thoracic pressure increases by a rapid closure of the glottis and simultaneous active expiration against this closed valve. In this phase, the laryngeal adductor muscles narrow or close the glottis completely; there is no flow, and the expiration muscles contract forcefully, which allows the subglottic pressure to build up (compression phase). Third, initiating the expulsive phase, an abrupt opening of the glottis combined with a forceful contraction of the expiratory muscles leads to rapid expulsion of air (expulsion phase). The airflow might be interrupted by intermittent glottic closures, a cough epoch, consisting of consecutive compressive and expulsive phases without intermediate inspirations. Effective cough is a highly dynamic phenomenon, requiring muscular strength and fine-tuned coordination of inspiratory, expiratory and laryngeal muscles.
Without glottic closure and opening, cough is not a cough, but a forced exhalation. When the expiratory muscles contract against a closed glottis, the built up pressure is approximately 50 to 100% greater than that obtained during other forced expiratory maneuvers in which the glottis is open. Laryngeal closure and opening connects to cough peak flow (CPF), the highest measured airflow spike during cough, appearing immediately after opening of the glottis during the cough cycle. Duration of the cough compression phase has been suggested to primarily manipulate the pace of cough (fast/slow), whereas CPF affects the power of cough (strong/weak). The threshold for clinically effective secretion removal has been proposed at CPF of 160-180 l/min. CPF constitutes the most commonly used measure to determine the effect of spontaneous or assisted cough in persons with NMDs. This rests on clinical work made by Barach in the 1950s. Later, it has been discussed whether other parameters might be more precise.

**The dysfunctional larynx**

The protective laryngeal reflexes may disturb voluntary actions and even become counterproductive for other important functions, and thereby create a "dysfunctional" larynx. Common respiratory symptoms like shortness of breath and abnormal breath sounds that are caused by laryngeal dysfunction may mimic symptoms of pulmonary diseases. This may confuse respiratory care professionals, and lead to laryngeal dysfunction being overlooked.

In the critically ill, the larynx is commonly dysfunctional following endotracheal extubation, possibly due to the rigid endotracheal tube impairing the reflex response patterns of the extremely sensitive laryngeal area. Chronic neurological diseases, such as ALS, Spinal Muscular Atrophy (SMA), Cerebral Palsy and Parkinson, may affect the function of bulbar innervated muscles. Malfunctioning sensory afferent nerves and abnormal reflex responses
impair muscle coordination, causing weakness or spasms. This disturbs speech, cough and swallowing.

In persons with ALS and bulbar involvement, MI-E may fail to increase CPF. Tabor-Gray et al. explored voluntary cough in ALS, stating that subjects with ALS cough differently compared to the healthy, and that both inspiratory and expiratory airflows are affected. The inspiratory phase is prolonged with a reduced peak flow rate, and the expiratory rise time is increased with lower peak flow rates. (Figure 2). This results in reduced cough volume acceleration, a gradual loss of adequate cough flow spikes and lower CPF values.

Furthermore, the larynx might not be able to respond appropriately to the external airway pressures that are applied during non-invasive positive pressure ventilation (NIV). Delguste et al. found complete upper airway obstruction with NIV-induced hypocapnia in three of four examined subjects treated with long-term NIV. It was suggested that the positive pressure-induced hyperventilation increase upper airway resistance. Jounieaux et al. found progressive glottic narrowing with positive pressure ventilation in healthy awake subjects, particularly in the absence of diaphragmatic activity. This increased inspiratory resistance, and thereby reduced the fraction of air delivered to the lungs. This situation was aggravated during stable sleep, and even more so during deep sleep. Georges et al. observed immediate obstruction from the tongue base during NIV in subjects with ALS. The most frequent solution was to reduce upper airway collapsibility by increasing the Expiratory Positive Airway Pressure (EPAP) to high levels, however, this was not always effective. Studies in lambs support these findings, indicating increased activity of laryngeal adduction muscles during NIV. One study that examined glottic patency during NIV in individuals with chronic obstructive lung disease (COPD) is in apparent conflict with these findings and with earlier studies. Oppersma et al. found that neither the inspiratory pressure level nor the inspiratory flow pattern did affect glottic patency in subjects.
with COPD. The authors postulated that this could be due to reflex pathways in subjects with COPD being different from those in healthy subjects, due to chronic exposure to CO₂ or by tobacco smoking harming their receptors’ response to chemical stimuli.⁷⁸

Laryngeal function is complex, carefully modulating and safeguarding the entrance to the airway tree, and serving several vitally important functions. We are far from understanding the complex interplays of all laryngeal functions, both in health and disease.

**LITERATURE REVIEW**

We searched for literature on assessment and interpretation of upper airways responses to MI-E. The review is based on repeated searches of the Medline database (accessed through PubMed), using the terms (with synonyms) "Mechanical Insufflation-Exsufflation" and "upper airway responses", focusing on studies including either clinical outcomes or laryngeal models. Studies describing either the methods used to assess the upper airways in combination with MI-E, or the upper airway responses to MI-E, were of interest. Furthermore, we reviewed reference lists of relevant studies. Papers written in English were considered. Studies are presented mainly in chronological order, but subcategorized by the examination method used. Ten studies addressing both the assessment and findings were identified (*Table 1*). Additionally, some studies discussed the role of the glottic closure and opening in the MI-E therapy without assessing it.

As one of the first to set focus on upper airway responses during MI-E therapy, professor JR Bach introduced the term "exsufflation-associated airway narrowing or collapse during MI-E treatment" in 1993, assuming this phenomenon disturbed MI-E treatment efficacy in subjects with reduced upper airway control.⁶ Both airflow curve detection, Computerized Tomography
(CT) scanning, and Transnasal Fiberoptic Laryngoscopy (TFL) have been applied to assess the upper airways during MI-E therapy, and bench testing with laryngeal models has been performed. One case report included the use of video-fluoroscopy prior to - and after the use of MI-E. To our knowledge, one review on upper airway function and responses to MI-E and NIV, focusing alone on TFL as mode of examination, has been published previously by Conde et al.79

**Computer Tomography (CT) scanning**

Sancho et al. are pioneers in systematically examining cough efficacy in subjects with ALS. In 2004, they examined the effect of MI-E in subjects with non-bulbar and bulbar ALS. MI-E generated clinically effective CPF in stable subjects, but not in those with bulbar dysfunction or with maximal insufflation capacity less than one liter and CPF <160 L/min.25 Similar to Bach’s postulation,6 they proposed severe upper airway collapse during exsufflation. Three subjects with ALS were studied by upper airway (pharynx and oropharynx) CT scanning at baseline and during exsufflation. Failure to increase CPF adequately was associated with dynamic collapse of the upper airway during exsufflation. They suggested that coordinated glottic movements and intact bulbar function are key elements for MI-E efficacy.25

**Transnasal Fiberoptic Laryngoscopy (TFL)**

Andersen et al. introduced dynamic TFL during MI-E (Figure 3 and 4) as a method in 2013, describing laryngeal response patterns to MI-E in healthy volunteers compatible to those described in normal cough.80 Healthy subjects initially abducted glottis both during insufflation and exsufflation, and displayed coordinated glottic closure when instructed to cough. When instructed to exhale during exsufflation, the glottis stayed open in the majority. However, subsequent to an initial abduction, various obstructing laryngeal movements were observed during insufflation, such as adduction of the vocal folds, retroflex movement of the epiglottis, and backwards movement of the tongue base, as well as hypopharyngeal
constriction during exsufflation (*Table 2*). The researches advocated that MI-E should not be thought of as a device that simply "fills up" and "empties" the lungs.80

In 2017, Andersen’s group published a cross-sectional study of laryngeal response patterns to MI-E in subjects with ALS and healthy controls.23 Supraglottic structures (aryepiglottic folds) adducted in subjects with ALS and bulbar symptoms, especially during insufflation (*Table 2B*) with high pressures; response patterns that clearly contrasted the inspiratory abduction observed in subjects with non-bulbar ALS and healthy controls. They suggested these responses might explain failure of MI-E treatment in persons with bulbar ALS, as the compromised laryngeal inlet obstructs inspiratory airflow during the initial phase of cough. The study also revealed that subjects with ALS without bulbar symptoms not always coordinated their laryngeal movements during MI-E cycles. In all subjects with ALS (with or without bulbar symptoms), short initial abduction of true vocal folds was followed by subsequent adduction during insufflation and exsufflation (*Table 2A*). Backward movement of the tongue base was prominent (*Table 2D*) and hypopharyngeal constriction during exsufflation (*Table 1E*) was observed in all.23 Please see *Table 2* and *Supplemental Video*.

In 2018, the same group24 described laryngeal response patterns to MI-E with disease progression, following subjects with ALS for up to five years. The first signs of laryngeal adduction (aryepiglottic fold adduction, *Table 2B*) occurred with the highest insufflation pressures and prior to any clinically evident signs of bulbar involvement (*Figure 5*). Cough became less expulsive, and was paralleled by laryngeal adduction occurring also at lower insufflation pressures. Backward movement of the tongue base (*Table 2D*) appeared in most, retroflex movement of the epiglottis (*Table 2C*) was observed in half of the cases. Hypopharyngeal constriction during exsufflation (*Table 2E*) was observed in all, but later in the disease progression than adverse events during insufflation. Triggering of swallowing
reflexes by the positive MI-E pressure further complicated these matters. Customized use of MI-E, with lower insufflation pressures and flows and patient triggered insufflations, led to less laryngeal adduction. This prolonged the time for which the treatment was perceived efficient by the subjects with ALS, thus, facilitated elongated successful use of MI-E.\textsuperscript{24}

The laryngeal role with respiratory therapies in children has been less studied, but nonetheless, it is equally important. Vollæt\ae{}r et al\textsuperscript{81} described a 12-month-old SMA Type I case with periodic problems with the MI-E device, with difficulties inflating the chest and mobilizing secretions. TFL during ongoing MI-E revealed signs of aspiration, as well as laryngeal closure during insufflation in response to high inspiratory pressures, thus, indicating bulbar affection – in line with the clinical observations. This is similar to what was previously observed in adult subjects with ALS.\textsuperscript{23, 24} The examination with TFL was well tolerated, and the findings led to immediate and targeted adjustments of the MI-E.\textsuperscript{81}

\textbf{TFL and Videofluoroscopy}

Allen et al.\textsuperscript{21} described a case with myotonic dystrophy type 1 with dysphagia and cough failure, aiming to shed light on secretion retention in the upper airways and how use of MI-E affects this. Three hospital admissions were registered following MI-E treatment initiation. TFL and videofluoroscopy prior to and after MI-E treatment were performed, revealing food and drink material entering the lower airways. The authors argued that implementation of MI-E without exploring dysphagia and bulbar impairment may have caused recurrent aspiration, and persistence of the subjects’ respiratory symptoms.\textsuperscript{21}

\textbf{Airflow curve registration}

Airflow curve registration during spontaneous breathing is widely used to diagnose sleep-apnea.\textsuperscript{82, 83} As lung insufflation and exsufflation require an adequately sized laryngeal inlet,\textsuperscript{37} one may assume that visually observed laryngeal adduction causes airflow obstruction, influencing treatment efficacy.\textsuperscript{9, 10, 56, 84} Elaborating on Bach’s postulation of exsufflation
being the main challenge, Lacombe et al.\textsuperscript{84} analyzed exsufflation airflow curves to subjects with NMDs. Following PCF, they described an abrupt flattening, or a flow decrease during exsufflation, assumed to indicate upper airway collapse. They introduced the parameter effective cough volume (ECV), defined as the volume exhaled above CPF >180 l/min. Even though the upper airways were not directly observed, they postulated that low ECV indicates upper airway collapse with 100% sensitivity and specificity. It was suggested that using CPF alone failed to detect upper airway collapse during negative pressure titration in MI-E, and that studying the complete exsufflation airflow curve, not just the peak value, could reveal laryngeal opening or closure.\textsuperscript{84}

When comparing flow curves and visualized laryngeal events during MI-E, preliminary findings from Andersen et al\textsuperscript{85} indicate that efforts to cough or exhale during exsufflation affect flow curve geometry (shape). The authors were unable to link visualized laryngeal response characteristics to unique airflow geometry patterns, but recognized several MI-E airflow geometry patterns (Figure 6).\textsuperscript{85} Vollsæter et al\textsuperscript{81} studied air-flow and pressure patterns registered by the MI-E device following the examination with TFL during ongoing MI-E, see Figure 7. Air-flow patterns registered by the MI-E device revealed altered insufflation flow geometry with the initial settings, improving after modifying the flow and pressure.\textsuperscript{23, 24}

**Laryngeal models**

Physical and mathematical models may simplify the complex structures of the human larynx. Paz with coworkers\textsuperscript{86} used an advanced computational model of the upper airways, the "Eulerian wall film model", based on realistic upper airway geometry including epiglottis, glottis and vocal fold movements resembling a healthy human. An MI-E device reduced mucus thickness in the upper airways (Figure 8). The results indicated that viscous shear force was the main mechanism clearing secretions, neither glottic closure time nor epiglottic position had significant effect. The cough efficiency was almost unaffected by the time of
laryngeal adduction as long as the inspiration phase was sufficiently effective. The MI-E device improved viscous shear force and the enhancement rate grew logarithmically with the operating pressure.  

Lachal et al. used a lung simulator with several resistance-compliance models and a latex tube to mimic laryngeal collapsibility. They simulated various respiratory conditions to explore the role played by the upper airways while using MI-E. Contrary to what was expected, CPF was higher with the collapsible tube. The generation of peak expiratory flow (PEF) occurred within the first 100 milliseconds of exsufflation, leading the authors to hypothesize that flexible tube walls accelerate the flow-increase during exsufflation.

DISCUSSION

Summary of the findings
In this narrative review, we focus on methods to assess upper airways during MI-E therapy and summarize the current state of the art of responses. The interpretation of findings and the following recommendations are based on the available literature as well as the author’s personal experiences. Enhancing the success rate of MI-E and NIV is of major clinical importance to vulnerable patient groups with devastating diseases, but our knowledge of upper airway responses to respiratory therapy is still limited. Due to the nature of diseases like ALS, clinical studies include small populations. Direct observations with TFL indicate that laryngeal function is highly important to MI-E treatment efficacy. Laryngeal bench models have shortcomings in imitating the complexity and dynamicity of the upper airway, but may enhance our understanding of airflow dynamics, and a wide range of MI-E settings may be systematically applied to suggest possible combinations to be applied subsequently in patients.
The dogma that upper airway collapse during exsufflation causes MI-E treatment failure, highly influenced former evaluation methods, assessing the exsufflation phase alone. Sancho et al.’s CT-scannings and Lacombe’s flow-curve shapes confirmed Bach’s postulate that exsufflation caused upper airway collapse in subjects with bulbar dysfunction. Later studies indicate that this exsufflation-related hypopharyngeal narrowing occurs also in the healthy. A certain narrowing is beneficial, increasing linear airflow velocity and shear forces that move secretions proximally. However, the studies of Bach, Sancho et al. and Lacombe et al. have been essential, introducing the vital understanding that MI-E airflows and pressures delivered via the upper airways may cause structural responses. In studies where the larynx was visualized during the whole MI-E cycle, adduction of laryngeal structures during insufflation was revealed in subjects with bulbar ALS, the opposite of the findings in non-bulbar subjects and healthy controls. A compromised laryngeal inlet during insufflation will obstruct inspiratory airflow, and lead to reduced filling of the lungs during the first phase of cough. This again will compromise the expiratory cough phase, conceivably creating a vacuum in the upper airways during exsufflation that leads to inefficient MI-E. This line of thinking turns the picture around - the observed exsufflation challenges might be a consequence of laryngeal inspiratory closure rather than the cause of treatment failure.

The airflow passing through the laryngeal lumen must obey simple physical laws; when airflow or turbulence exceeds a critical value, the pressure within the structure that confines the airflow must decrease, and deformations of that structure will eventually occur. Structural deformation subsequently affect the airflow, a situation labelled "flow-structure interactions" by physicists. In the human larynx, reflex mechanisms as well as voluntarily controlled neuromuscular interactions add complexity to this model. MI-E pressures may provoke disadvantageous laryngeal movements, and the supraglottic area seems most prone to collapse. Therapeutic use of positive pressures provoke laryngeal narrowing. Thus, it
is not surprising that positive insufflation pressures during MI-E promote laryngeal closure in individuals with ALS.23, 24 ALS affects motor neurons in the brain and spinal cord. Both afferent and efferent innervation may play a part, laryngeal reflex circuits may be hypo-responsive or hyper-responsive or dysregulated,90-92 and loss of motor control and strength, spasticity, and sensory insufficiency in the laryngeal muscles further reduce laryngeal control.90, 93, 94 Inefficacy of MI-E treatment is multifactorial and vary individually. This research field is still in an "embryonic" phase. Further assessment of upper airway responses during the complete MI-E cycle is crucial to understand these complex interactions. We acknowledge and certainly encourage future research in this field.

Where should we go from here?

TFL was previously a specialized tool used in otolaryngology clinics. It is presently used in several functional contexts, like during swallowing,95 inspiratory muscle training96 or exercise tests,97, 98 being performed by medical doctors, speech therapists and other trained health professionals. Sayas Catalàn et al.74 postulated that NIV titration by TFL led to fewer obstructive events in subjects with upper-airway obstruction. The knowledge of upper airway responses during MI-E in the pediatric population is scarce and should be targeted. One clinical case report81 and our clinical experience with single cases support that TFL is feasible and tolerated also in small children, especially in those familiar to airway suction through the nose. In preterm infants with dysphagia, simultaneous video-fluoroscopy and TFL in evaluation of swallowing has been proposed feasible and with higher diagnostic yield than each procedure done separately.99

We believe that TFL performed during ongoing non-invasive respiratory therapies improve our understanding of laryngeal responses, and aids tailoring and individual optimizing of treatment (Table 3). However, TFL examination during MI-E has limitations. It is an invasive procedure requiring skilled hands, and may be judged unpleasant. During MI-E manoeuvres,
the larynx tend to move upwards, requiring adjustments of the position of the laryngoscope. Anatomical structures may preclude visual access, like a high standing epiglottis or a narrow hypopharynx. Supraglottic adduction by nature obscures the view of the glottis. Airway secretions may obscure the view, and therefore pre-treatment to clear secretions should be considered. To produce adequate recordings, several MI-E cycles may be required.

Alternatives to TFL should be explored. CT-scanning applies ionizing radiation, is expensive, stationary and hardly dynamic. Simple throat auscultation may gain information of laryngeal airflow and synchronization of glottic closure to MI-E cycles, similar to cervical auscultation used to evaluate swallowing. Ultrasound imaging may visualize laryngeal structures, and a study of laryngeal responses during MI-E and NIV combining both TFL and ultrasound is planned to explore the validity of ultrasound as a diagnostic tool in this context (Clinicaltrials.gov ID: NCT04586855).

To what extent laryngeal adduction observed during MI-E influences the expiratory airflow velocity, which is crucial to move secretions, represents an important functional issue. Simultaneous monitoring of airflow curves and laryngeal movements during MI-E could reveal more information. Potential mask leaks, and the fact that the relationship between the structural responses in the upper airways and the airflow shapes still remains poorly understood, may interfere.

**CLINICAL IMPLICATIONS**

As alluded to by Simonds; individuals with poor laryngeal control may not have failed their MI-E therapy, but instead the therapy may in fact have failed them. It is reasonable to assume that when the MI-E cycles are in synchrony with the upper airway responses, this will improve the success rate of MI-E.
**Individualizing MI-E treatment**

MI-E use should be customized, and altered in the individual with counterproductive upper airway responses. See Figure 9. Generally, the inspiratory airflow should not enter the upper airways too abruptly. High inspiratory pressures may generate laryngeal closure, thus, pressures should be gently titrated upwards. Asymmetric settings with lower positive insufflation pressure than the corresponding negative exsufflation pressure used in the same respiratory cycle may be combined with lower insufflation flows. Increasing inspiratory time may be necessary to achieve the required insufflation volume prior to exsufflation.23, 88, 103 A prolonged inspiration seems to be physiological in inducing cough.68 Several rapid MI-E cycles may be challenging or impossible to handle for individuals with bulbar dysfunction. Successful treatment requires that the larynx is "reset" after exsufflation, and swallowing or closing reflexes should be brought to an end before the next insufflation. An increased time interval between exsufflation and insufflation, or the use of one cough cycle at a time, might be appropriate to prepare the larynx for the next insufflation.24 Dynamic TFL during ongoing MI-E could be a valuable and well-tolerated tool to further optimize treatment, providing direct anatomical views and potential aspiration tendency, as well as feedback on treatment responses.23, 24, 104 It will be important to perform further studies to provide a variety of subjects with the best possible treatment titrated in the most precise way.

**Effect outcomes for airway clearance in individuals with poor laryngeal control**

The important questions are, will individually optimized MI-E treatment assist the airway secretion clearance in individuals with poor laryngeal control, and how can this be measured? Efficient laryngeal closure and opening connects to the CPF,56 hence individuals with poor laryngeal control fails to create a prominent expiratory flow peak.68 We should consider
whether CPF is an appropriate effect outcome measure for airway clearance in those with poor laryngeal control.

Andersen’s findings emphasize the importance of keeping the larynx open to achieve a sufficient insufflation volume prior to cough and to allow both volume- and flow acceleration to move the secretions. Simulations with advanced laryngeal models indicate that MI-E does achieve effective shear forces even with a fixed glottic opening, but glottic closure and opening significantly improves this. Volpe et al. emphasized the importance of expiratory flow bias on secretion movement, indicating that the relation and difference of peak insufflation and exsufflation flows influence upstream secretion movement. Expiratory flow bias and MI-E pressure gradients correlated significantly with mucus displacement, whereas CPF did not. In addition to keeping laryngeal structures open, lower insufflation flows might increase expiratory flow bias and, consequently, the efficacy of clearing secretions. The CPF phase accounts for only 25% of the cough shearing force, and the sustained flow rate which occurs after this is probably of great significance. Lacombe’s group suggested there is a volume dependent factor of ECV that may detect upper airway obstruction, and they also suggested a time-dependent efficacy factor during exsufflation, defined as effective cough time (ECT); the time spent above CPF >180 L/min.

To conclude, judging MI-E efficacy is complex. The key element is that the upper airways must allow the air to flow in and out of the lungs. Measurements of flow bias, cough velocity, effective cough time and cough volume, and upper airway structural responses will add further clinically important information. In the long run, treatment compliance and Quality of Life, as well as rates of infections, exacerbations, and hospitalizations should be studied. One should aim at always optimizing and tailoring MI-E settings individually in each person.
SUMMARY

The larynx is a highly complex organ that carefully modulates and safeguards the airway entrance. In individuals with poor laryngeal control, therapeutic positive pressures may provoke disadvantageous laryngeal responses, precluding air filling of the lungs and compromising attempts to assist the expiratory phase of cough. This leads to inefficient MI-E therapy and discomfort. Great care must be taken to avoid applying pressures and cough cycles that the larynx is unable to handle. Video-recorded flexible transnasal laryngoscopy is feasible to characterize laryngeal responses throughout MI-E and NIV interventions. Individually adjusted settings may prevent adduction of laryngeal structures during insufflation, and thus prolong successful use of MI-E and possibly also NIV. Currently, in our opinion, direct laryngeal visualization during treatment is the best and most objective approach in most challenging subjects.
REFERENCES

1. Fink JB. Forced expiratory technique, directed cough, and autogenic drainage. Respir Care 2007;52(9):1210-1221; discussion 1221-1213.


FIGURE LEGENDS

Figure 1. Superior, posterior and medial views of the larynx with anatomical landmarks and the laryngeal levels of the hypopharynx, supraglottis, glottis, subglottis and trachea.

Figure 2. Voluntary cough spirometry waveform depicting A) cough flow with distinct inspiratory and expiratory parameters in a healthy individual, depicting the three primary phases of cough from which objective temporal airflow parameters are computed and aberrant. Cough flow in two individuals with ALS with B) spinal-onset and C) bulbar-onset disease type. Adapted from reference,68 with permission from Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration.

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Figure 4. The TFL examinations were recorded using two continuously running and synchronized video streams on one screen, depicting the laryngeal view in one (right) and the various phases on the MI-E device in the other (left). Anatomic landmarks are illustrated on the laryngeal view. Abbreviations: TFL= Transnasal Fiberoptic Laryngoscopy, MI-E= Mechanical Insufflation-Exsufflation. From reference,24 reproduced with permission from BMJ Publishing Group Ltd.
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**Figure 7.** Depicted flow and pressure curves from the mechanical insufflation-exsufflation (MI-E) device with high inspiratory pressures (+35 cm H₂O) when the larynx closes at inspiration (left), and at lower inspiratory pressures (+25 cm H₂O) when the larynx stays open during inspiration (right). From reference⁸¹ reproduced with permission from Clinical Case Reports.

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Table 1. Study design, sample size, method used to assess the upper airways and to use MI-E. Studies are divided to clinical- and bench studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Population</th>
<th>Upper airway assessment method</th>
<th>MI-E Intervention</th>
</tr>
</thead>
</table>
| Sancho et al 2004  | Additional examination in cross sectional study examining the effect of MI-E in ALS | N=3: ALS (adults; age not stated)                | CT scanning of upper airways during baseline and exsufflation. Visual interpretation of the CT scans and calculation of diameter reduction from baseline to exsufflation.                                                                 | Pressure: ±40 cm H₂O  
Insufflation flow: on  
MI-E cycle time: 2s Insufflation / 3s Exsufflation / 1s Pause  
Instruction: To keep the airway open but otherwise remain passive. |
| Andersen et al 2013| Cross-sectional observational study | N=20: Healthy volunteers (24.2±1.9)             | Video-recorded TFL during ongoing MI-E. Visual interpretation of the video-recordings and preparation of an observation scheme; thereafter all the observed movements were assessed.                                                                 | MI-E protocol with various combinations of pressures, instructions and manual thoracic thrusts.  
Pressures: ±20, ±30, ±40, and ±50 cm H₂O  
Insufflation flow: high  
MI-E cycle time: 2s Insufflation / 3s exsufflation / 1s Pause  
Instruction: Always to active inhale (but not too deep). Both to active exhale and cough. |
| Andersen et al 2017| Cross-sectional observational study | N=40: 20 ALS (68.7±9.3) and 20 healthy volunteers (66.9±7.2) | Same as in 93                                                                                                                                  | Same as in 93                                                                 |
| Andersen et al 2018| Prospective longitudinal observational study | N=13: ALS (67.1±8.5)                                                                 | Same as in 93                                                                                                                                  | Same as in 93 and additionally:  
Patient-triggered insufflation: on and off  
Oscillation: frequency 5 and 10 Hz, amplitude 5 and 10 cm H₂O  
Asymmetric use of pressure settings: Positive pressure range +15 to +40 cm H₂O combined with |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>N, Diagnosis</th>
<th>Methods</th>
<th>Findings/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al 2018</td>
<td>A case report</td>
<td>N=1: DM1 (21)</td>
<td>Video-recorded TFL prior and post MI-E: Visual interpretation of swallowing, volitional coughing, pooling of secretions, food and fluids from pharynx to larynx. Videofluoroscopy prior and post MI-E: Visual interpretation of material movement from upper airways to lower airways. Flow-volume curve registration during MI-E. Interpretation of flow curve: Detected abrupt flattening or flow decrease vs previous less negative exsufflation pressure after CPF. Categorized with three exsufflation flow profiles. Measurement of ECV.</td>
<td></td>
</tr>
<tr>
<td>Lacombe et al 2019</td>
<td>Prospective observational study</td>
<td>N=27: NMDs (DMD, CMS, CMT, LGM, SMA, MM) (30.6±9.2)</td>
<td>Same as in 24 and additionally concurrent flow- and pressure registration during TFL and MI-E: Airflow and pressure signals were evaluated on a cough-by-cough basis, and patterns were described and categorized. Airflow geometry pattern categories were paired and compared to visualized laryngeal events and to participant category.</td>
<td>Same as in 24 and additionally air-flow patterns registered by the MI-E device were studied.</td>
</tr>
<tr>
<td>Andersen et al 2020</td>
<td>Explorative longitudinal descriptive observational study</td>
<td>N=23: 13 ALS (68±7.7) and 10 healthy volunteers (63.5 ±5.1)</td>
<td>Same as in 80 and additionally concurrent flow- and pressure registration during TFL and MI-E: Airflow and pressure signals were evaluated on a cough-by-cough basis, and patterns were described and categorized. Airflow geometry pattern categories were paired and compared to visualized laryngeal events and to participant category.</td>
<td>Same as in 80 and additionally air-flow patterns registered by the MI-E device were studied.</td>
</tr>
<tr>
<td>Vollneter et al 2021</td>
<td>A case report</td>
<td>N=1: SMA (1)</td>
<td>Same as in 80 and additionally air-flow patterns registered by the MI-E device were studied.</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Insufflation flow: high, medium and low
- Pressure: +10 cm H₂O and -40 cm H₂O
- MI-E cycle time: Administratively adjusted manually.
- Instruction: n/a
- Pressure: Individually adjusted from +10 cm H₂O to maximum of +40 cm H₂O, where the lowest inspiratory capacity was chosen (from +24 to +40 cm H₂O).
- Exsufflation pressure was individually adjusted from -20 cm H₂O to -70 cm H₂O, where the pressure producing the highest volume exsufflated at flow >180L/min was chosen (from -40 to -70 cm H₂O).
- MI-E cycle time: 2.5s Insufflation / 2.5s Exsufflation / n/a Pause
- Instruction: Strong encouragement to actively cough

**References:**
- Allen et al 21
- Lacombe et al 84
- Andersen et al 85
- Vollneter et al 81
Insufflation flow: Medium and Low
MI-E cycle time: 1.8s Insufflation / 1.2s Exsufflation / 1s Pause
Instruction: To breathe in and to cough.

Paz et al. 2017
Bench study
Computational laryngeal model based on realistic geometry, epiglottis and glottis with dynamic mesh method (considering different abduction and adduction angles and velocities).
Computational Eulerian wall film model. Calculation of deformation of the flexible tissue and properties for the mucus movement.
Pressure: Increased from ±5 to 40 cm H₂O with a steps of 5 cm H₂O
Insufflation flow: n/a
MI-E cycle time: n/a
Not a commercial MI-E device was used.

Lachal et al. 2019
Bench study
Laryngeal model (with and without collapsible latex tube) combined with lung simulator with resistance of 5 and 20 cm H₂O/L/s, and compliance of 20, 40, and 60 L/cm H₂O.
Measurement of pressure and flow, where primary outcome was PEF.
Pressure: ±30, ±40, and ±50 cm H₂O
Insufflation flow: n/a
MI-E cycle time: 3s insufflation / 3.2s exsufflation / 2s pause

MI-E=Mechanical Insufflation-Exsufflation, ALS=Amyotrophic lateral sclerosis, CT=Computer Tomography, TFL=Transnasal fiberoptic laryngoscopy, DM1=Congenital myotonic dystrophy type 1, NMD=Neuromuscular disorders, DMD=Duchenne muscular dystrophy, CMS=Congenital myasthenia gravis, CMT=Charcot-Marie-Tooth, LGM=Limb girdle muscular dystrophy, SMA=Spinal muscular atrophy, MM=Mitochondrial myopathy, CPF=Cough peak flow, ECV=Effective cough volume, PEF=Peak Expiratory Flow
Table 2. Five laryngeal events (panels A through E) during MI-E defined as adverse and typical bulbar features based on findings in the studies of Andersen et al.\textsuperscript{23,24,81}, contrasting normal cough. Abbreviations: MI-E= Mechanical Insufflation-Exsufflation. From reference,\textsuperscript{24} reproduced with permission from Respiratory Care.

<table>
<thead>
<tr>
<th>Response</th>
<th>Laryngeal level</th>
<th>Adverse laryngeal response during MI-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Glottic</td>
<td>Adduction of true vocal folds during insufflation; paradoxical movement of true vocal folds during inhalation creating either a slim glottic opening or a total glottic closure.</td>
</tr>
<tr>
<td>B</td>
<td>Supraglottic</td>
<td>Medial rotation of the cuneiform tubercles accompanied by considerable adduction of the aryepiglottic folds during insufflation, to the extent that it prevents observation of the glottic laryngeal level below.</td>
</tr>
<tr>
<td>C</td>
<td>Epiglottis</td>
<td>A retroflex movement of the epiglottis (a passive dorsal rotation) covering the glottis, either as a brief movement or lasting throughout the insufflation.</td>
</tr>
<tr>
<td>D</td>
<td>Hypopharyngeal</td>
<td>Backward movement of the tongue base during insufflation constricting the laryngeal entrance.</td>
</tr>
<tr>
<td>E</td>
<td>Hypopharynx</td>
<td>A severe hypopharyngeal narrowing during exsufflation.</td>
</tr>
</tbody>
</table>
Table 3. Aspects to guide laryngeal evaluation with dynamic TFL during MI-E.

<table>
<thead>
<tr>
<th>Dynamic TFL examination during MI-E therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess the drooling/pooling of secretions, and how does the therapy affect this?</td>
</tr>
<tr>
<td>Retention/aspiration of saliva and/or secretions</td>
</tr>
<tr>
<td>Is the laryngeal response to MI-E normal?</td>
</tr>
<tr>
<td>In case of abnormal laryngeal responses, determine the location of the counterproductive response:</td>
</tr>
<tr>
<td>Hypopharynx, Epiglottis, Base of the Tongue, Aryepiglottic Folds, True Vocal Folds</td>
</tr>
<tr>
<td>Describe the abnormal response/movement:</td>
</tr>
<tr>
<td>Abduction, Adduction: Constriction or Collapse</td>
</tr>
<tr>
<td>Detect the phase of the MI-E cycle where the counterproductive response appears:</td>
</tr>
<tr>
<td>Insufflation, Pressure drop, Exsufflation</td>
</tr>
<tr>
<td>Detect the onset of the counterproductive event:</td>
</tr>
<tr>
<td>Immediately/During</td>
</tr>
<tr>
<td>Identify the frequency of the counterproductive events:</td>
</tr>
<tr>
<td>In all the cycles or in some cycles</td>
</tr>
<tr>
<td>Examine the response to altered therapy,</td>
</tr>
<tr>
<td>Fine-tune Insufflation settings (ensure triggering on every insufflation, decrease inspiratory flow, decrease inspiratory pressure, increase inspiratory time)</td>
</tr>
<tr>
<td>Other adjustments (describe)</td>
</tr>
</tbody>
</table>
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317x177mm (120 x 120 DPI)
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