

BMJ Open Adjustments of non-invasive ventilation and mechanically assisted cough by combining ultrasound imaging of the larynx with transnasal fibre-optic laryngoscopy: a protocol for an experimental study

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ABSTRACT

Introduction Application of non-invasive positive airway pressure may provoke laryngeal responses that obstruct the airways, especially in patients with disturbed laryngeal control. To control and adjust for this, transnasal fibre-optic laryngoscopy (TFL) is used to visualise laryngeal movements during therapeutic interventions. Being an invasive procedure, this may be unpleasant for patients. The aim of this study is to evaluate if ultrasound (US) imaging of the larynx may be used as an alternative less invasive diagnostic tool for evaluating the upper airway responses to non-invasive ventilation (NIV) and mechanical insufflation–exsufflation (MI-E).

Methods and analysis This protocol presents an experimental cross-sectional study of a novel method to study laryngeal responses in adult healthy volunteers (n=30). The participants will be assessed with simultaneous TFL and laryngeal US imaging (anterior and lateral approaches) during NIV and MI-E therapy. Additionally, airflow and pressure signals will be registered during the procedures. The primary outcome is whether laryngeal US is a feasible method to study laryngeal responses and, if so, to compare the laryngeal responses visualised with TFL and US. The participants' perception of the examinations will be recorded. Secondary outcomes include airflow curve shapes and calculated ventilation volumes during the interventions.

Ethics and dissemination The study has been approved by The Regional Committee for Medical Research Ethics in Norway, and registered in ClinicalTrials.gov. Results will be disseminated through peer-reviewed journals, presentation of scientific abstracts at international medical conventions and oral presentations in relevant medical conventions.

Trial registration number NCT04586855.

INTRODUCTION

Respiratory physiotherapy is a cornerstone in the care of patients with respiratory muscle weakness. Both ventilation and secretion

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first study to validate laryngeal ultrasound (US) imaging performed during ongoing non-invasive application of positive and negative airway pressures.
- ⇒ Laryngeal movement will be visualised and recorded simultaneously by laryngoscopy and US, and will be viewed in slow motion afterwards.
- ⇒ The investigators are not blinded during the data collection. However, during the interpretation of the material, the investigators will be blinded to the results from the other method.
- ⇒ The study is explorative and might not be sufficiently powered to assess outcome differences.

management may be supported mechanically by applying therapeutic positive/negative pressures to the airways via a mask (non-invasively). During such procedures, upper airway patency is crucial to allow air to flow freely in and out of the lungs.

The larynx is positioned in the upper airways and has a complex gateway function, protecting the airways from aspiration and controlling both phonation and ventilation.¹ The larynx may be divided into supraglottic, glottic and subglottic levels, and consists of airway mucosa, rigid cartilage skeletons, ligaments, and muscles for adduction and abduction. These structures together create a dynamic organ which is controlled by reflexes as well as voluntary movements. During quiet breathing, the abduction of the larynx is fundamental to allow free airflow in and out of the lungs at the least possible resistance.¹

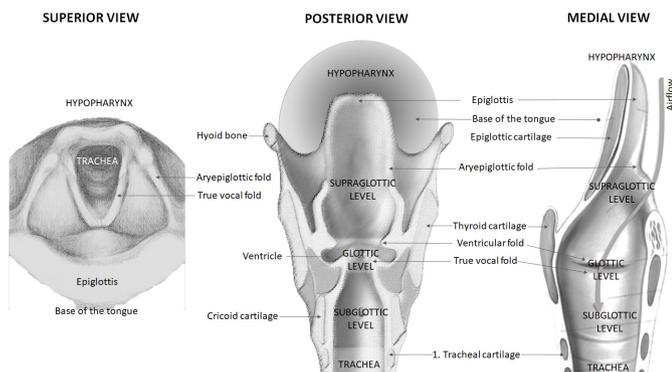


Figure 1 Superior, posterior and medial views of the larynx with anatomical landmarks. Published with permission from Andersen *et al.*¹

The larynx widens during inspiration and narrows during expiration²³ (see figure 1).

Air normally enters the lungs through the negative intrathoracic pressure within the thoracic cavity created when the respiratory muscles contract. Recent studies have shown that the larynx is vulnerable to adduct when positive/negative pressures are applied non-invasively to the airways. Thus, both in healthy volunteers and in patients with amyotrophic lateral sclerosis (ALS), the larynx has been shown to adduct and thus obstruct the airflow in response to positive/negative pressures applied during mechanically assisted cough treatment, most prominent in patients with ALS with bulbar symptoms.⁴⁻⁶ Similar responses have been demonstrated also during non-invasive ventilation (NIV).⁷⁻¹³ These findings may have consequences for all modes of non-invasive mechanical respiratory support that use positive and/or negative airway pressures, and notably also in patients with other diseases, such as chronic pulmonary diseases under critical care or in respiratory failure.^{14 15}

To date, transnasal fibre-optic laryngoscopy (TFL) is considered the gold standard to visualise the larynx.¹⁶⁻²³ TFL during ongoing non-invasive positive/negative pressure treatment is a feasible method to visualise upper airway responses, especially in patients who do not respond to treatment as expected.⁴⁻⁶ TFL may feel unpleasant for some patients; however, it is generally well tolerated by most. The patient who might be most challenging to examine with TFL typically have bulbar dysfunction, excessive secretions or general hypotonia, as these characteristics complicate proper visualisation of the laryngeal structures. Therefore, there is a need for less invasive techniques, and we hypothesise that laryngeal ultrasound (US) may provide an alternative diagnostic tool.

Diagnostic US is a non-invasive imaging technique. US equipment is generally readily available in most health-care facilities. It is widely used in a vast variety of conditions, is free from radiation and is not associated with pain or discomfort. US imaging has been used to evaluate the larynx, for example, to diagnose vocal fold dysfunction

following thyroid surgery or following intubation in intensive care patients.²⁴⁻²⁶

Whether laryngeal movements can be evaluated by US during positive/negative pressure treatment, or whether this method is as accurate as TFL, needs to be established. The aim of this study is to explore the feasibility and diagnostic accuracy of US imaging to evaluate laryngeal responses during NIV and mechanical insufflation–exsufflation (MI-E) treatment.

METHODS AND ANALYSIS

Study design

This is a cross-sectional study conducted in healthy volunteers to evaluate US imaging of laryngeal responses during ongoing NIV and MI-E.

Patient and public involvement

A user representative familiar with daily NIV and MI-E treatment was involved in the planning of the study. This has provided invaluable feedback regarding implementation and focus, ensuring the project's ability to capture patient-relevant needs and experiences.

Study setting and recruitment

A convenience sample of 30 healthy adult volunteers will be recruited among healthcare professionals and students. The study will be conducted in a lung function testing laboratory at a hospital. Exclusion criteria will be age <18 years or a history of bronchospasm or pneumothorax, or subjects with pronounced nasal obstruction. All volunteers will receive oral and written information about the study and must provide a written informed consent before entering the study. Participants can withdraw from the study at any time. Recruitment for the study will be undertaken from January 2022 to January 2023.

Outcomes

The study will assess feasibility and utility of laryngeal US imaging during NIV and MI-E. The primary outcome is the ability to accurately describe laryngeal movements and patterns during NIV and MI-E. Thereafter, we will compare the laryngeal responses visualised with TFL and US. The participants' perception of the examinations will also be assessed. Secondary outcomes include airflow curve registrations and calculated ventilation volumes during the NIV and MI-E.

Population characteristics

Gender, age, height and weight of the participants will be recorded.

Forced flow–volume curves will be obtained with Vyntus spirometer (Carefusion, Hoechst, Germany) according to European Respiratory Society guidelines.²⁷ Raw data will be standardised for age, height, sex and ethnicity, and will be presented as Z-scores and per cent predicted.²⁸

Peak cough flow (PCF) will be recorded with a handheld Peak Expiratory Flow metre (Vitalograph, Ennis,

Ireland) using a face mask, with the participant in seated position. The highest value from three or more attempts will be chosen.²⁹

Plateau values (average of 1 s) of the maximal inspiratory (PI_{max}) and expiratory (PE_{max}) muscle strength pressures will be measured in seated position with Respiratory Pressure Metre Micro RPM (Micro Medical, Rochester, England) with a mouthpiece. PI_{max} will be measured from residual volume, and PE_{max} will be measured from total lung capacity. The highest values from three or more attempts will be selected for analysis.³⁰

Interventions

A set protocol for MI-E (Cough Assist E70; Respironics, Murrysville, USA) and NIV (VPAP Stellar; Resmed, San Diego, USA) commonly used in therapeutic trials in patients. All participants will first be assessed during normal breathing and then asked to phonate 'eeee' to establish normal laryngeal movements as well as vocal fold closure.

NIV settings will be expiratory positive airway pressure of +4 cmH₂O combined with inspiratory positive airway pressure of +20 cmH₂O. The participants will breathe approximately 3 min with NIV.

MI-E settings will be insufflation–exsufflation pressures ± 40 cmH₂O. The participant will have five insufflation–exsufflations on each combination, one while being passive (instruction: 'Let the air just flow in and out of the lungs') and one with active coughing (instruction: 'Breathe slightly in and cough'). Each set takes approximately 30 s.

Examinations

The examinations will be performed in 1 day and take approximately 15 min. TFL, US imaging of the larynx, and recording of airflow and pressures will be performed simultaneously throughout all interventions (figure 2). Participants will be verbally informed prior to the examination and during the procedure. Thereafter they will be positioned with the back of the chair reclined in 40°, their neck slightly extended. US examinations will be performed in the same order during the interventions.

TFL visualisation of the larynx

A local anaesthetic spray (lidocaine, Accord Healthcare, Middlesex, Great Britain) will be used before insertion of the laryngoscope. The flexible laryngoscope (diameter 2.6 mm, ENF V.3; Olympus, Tokyo, Japan) is lubricated with local anaesthetic gel (lidocaine, Accord Healthcare) and led through a hole in a modified full facial mask (face mask for Cough Assist Ventilatory Circuit, Respironics), via the nose to the nasopharynx, and advanced until a satisfactory view of the larynx is obtained. The facial mask serves to fixate the laryngoscope.⁶ The TFL will send signals to a TV screen for continuous visualisation during the entire examination, and the position will be adjusted as required for optimal visualisation of vocal folds.



Figure 2 Set-up of the study with translaryngeal fibre-optic laryngoscopy and laryngeal ultrasound performed simultaneously during the whole intervention.

US imaging of the larynx

The laryngeal US imaging will be carried out by an experienced US investigator (GN) previously trained in laryngeal imaging of 30 adult cases including healthy normals and patients. The US device for laryngeal imaging will be the Vscan Air (GE Healthcare, General Electric Company, Massachusetts, USA). After applying ultrasonic gel, a linear US transducer (frequency 5–10 MHz) in a two-dimensional mode will be placed over the thyroid. We will adjust the depth and increase the gain as required for optimal visualisation of vocal folds.³¹

We will use the following methods for laryngeal US imaging. Anterior imaging identifies vocal fold movements,^{24–26} and lateral imaging identifies arytenoid movements³² (figure 3). First, the transducer will be placed transversely over the middle section of the thyroid cartilage to view the vocal folds and the arytenoid cartilage. Subsequently, the transducer will be placed vertically approximately 1.0–1.5 cm inside and parallel to the lateral border of the thyroid cartilage, along the oblique line. The transducer will be placed at both sides of the thyroid cartilage laminae, and movements of both arytenoid cartilages will be observed separately. The transducer will send signals to a tablet (Galaxy Tab V.S7; Samsung, Seoul,

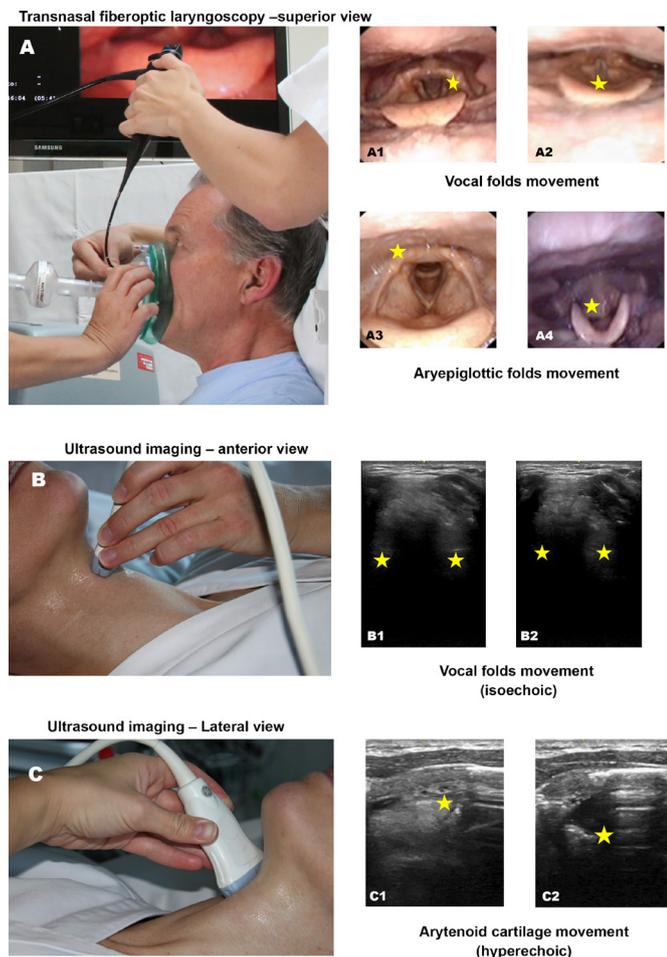


Figure 3 Set-up of translaryngeal fibre-optic laryngoscopy (A), anterior (B) and lateral (C) ultrasound with imaging of laryngeal movements of abduction (A1,A3,B1,C1) and adduction (A2,A4,B2,C2). Both interesting structures are marked with a star; vocal folds (A1,A2,B1,B2) and aryepiglottic folds (A3,A4,C1,C2).

South Korea) via Bluetooth for continuous visualisation during the entire examination. The imaging is visualised on the tablet during the intervention. The transducer will be adjusted as required for optimal visualisation of the targeted structures.

Video recording of the NIV/MI-E device

An external video camera (Sony SRG-300HW; Sony Computer Science Laboratories, Tokyo, Japan) with an attached microphone will document the NIV/MI-E device's control panel, with the instructions given by the therapist and the respiratory sounds produced by the participant. This will link the laryngeal images to the NIV/MI-E cycles.

Airflow and pressure registration

Airflow and pressure signals will be measured with a pneumotachograph (Hans Rudolph, Shawnee, USA) and differential pressure transducer (model MP 45; Validyne, Northridge, USA) inserted in the circuit between the face mask and the NIV/MI-E device, recording airflow, volume and pressure during the interventions (figure 4). Signals

are digitalised and sampled for analysis (Biopac, Goleta, California, USA) and run on a computer with AcqKnowledge Software V.5.0 (Biopac). Flow curve registration synchronous with TFL during NIV and MI-E will provide information on airflows, volumes and treatment pressures during the interventions. Constructed synchronised airflow and pressure curves are analysed with AcqKnowledge Software V.5.0.

Simultaneous recording of TFL, US, NIV/MI-E device panel, and airflow and pressure registrations

All four simultaneous recordings (TFL and US, airflow and pressure registration signals, and the NIV/MI-E device panel) will be sent via HDMI wires and Cam Links 4K (Corsair Memory BV, Almere, Netherlands) to one screen with Open Broadcaster Software (OBS V.26.1.1, 64-bit for Windows). The OBS will record all the simultaneous recordings as one video file and store it on the research server, allowing retrospective investigation of laryngeal events during the procedure. To ensure adequate technical quality of the recordings, the complete set-up is shown in real-time during the entire procedure on a computer screen present in the same room, at all times visible for all examiners.⁴⁻⁶

The video recordings from each participant will then be edited into a video file including 12 film clips based on representative shots of each intervention arm by a medical photographer. For blinded evaluation, three versions will be made:

- ▶ One recording containing all examinations.
- ▶ One recording blinded for US.
- ▶ One recording blinded for TFL.

Interpretation of the laryngeal visualisations

The TFL and US recordings will be assessed independently and blinded. Both video recordings will be reviewed and evaluated in real time and in slow motion. For TFL evaluation, we will use the same method as described in Andersen *et al*,⁶ but customised additionally for US evaluation. When comparing the laryngeal responses found by TFL and US, the direct TFL observations will serve as the gold standard to the used method described by Kandil *et al*.³³

Participants' perception of the examinations

A numerical rating scale of 0–10 (where 0 is no discomfort and 10 is the worst possible discomfort) will be used to evaluate the study participants' perception of each examination with TFL and laryngeal US.

Analysis of the data

Statistics

Data will be stored and processed in Stata V.17 for Windows. As this is an explorative study, power calculations have not been performed. We plan to report the analyses from the NIV and MI-E interventions separately.

Baseline characteristics will be presented as descriptive statistics in tables with means or medians, SD and ranges, as appropriate.

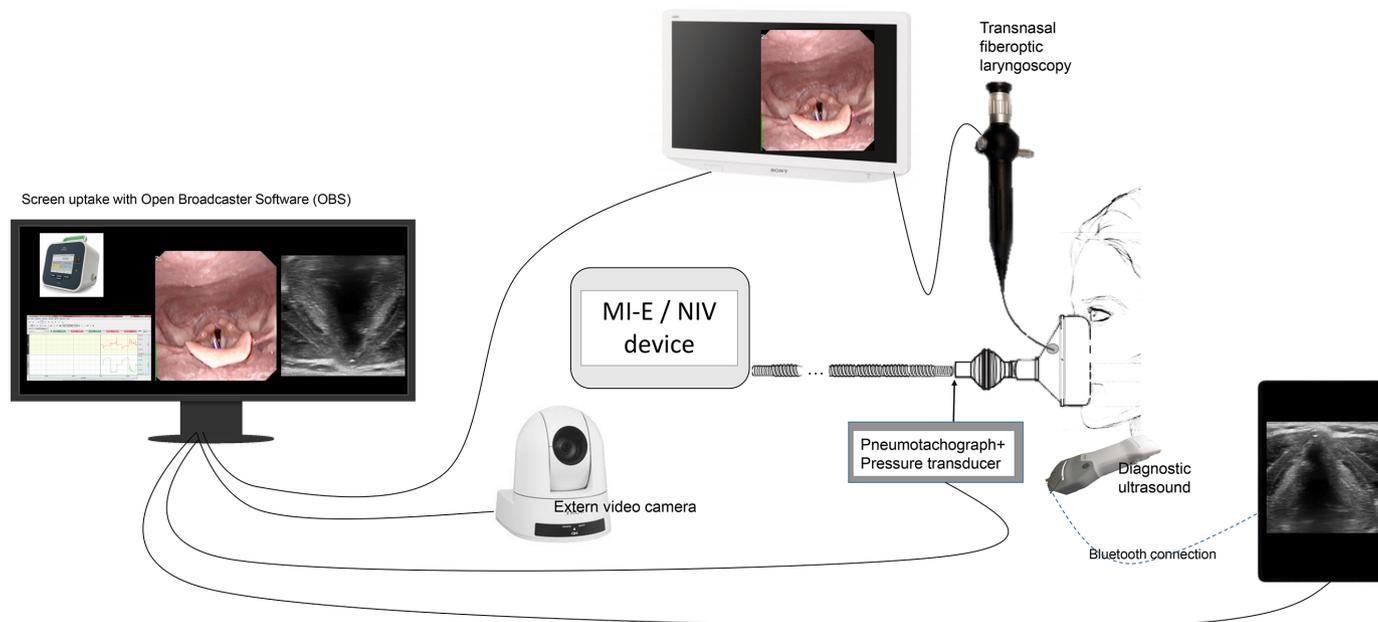


Figure 4 Set-up of all examinations with translaryngeal fibre-optic laryngoscopy, laryngeal ultrasound, airflow and pressure registration.

A true-negative finding is the detection of normal laryngeal movements by US imaging, whereas a false-positive finding is the inability to detect this normal movement. A true-positive finding is the ability of US imaging to detect dysfunctional laryngeal movements, whereas a false-negative finding is the inability to detect the dysfunctional movements. The χ^2 test, or Fisher's exact test, will be applied to assess differences between findings with TFL and US imaging, as appropriate.

As TFL is considered the gold standard to evaluate laryngeal movements; we will calculate sensitivity, specificity, accuracy, negative and positive predictive values of US compared with TFL.

The airflows, volumes and pressures will be compared in respect to PCF, effective cough time (ECT) and effective cough volume (ECV). ECT is defined as the time with PCF above 3 L/s, and ECV is defined as the volume exhaled at a flow >3L/s (180L/min).^{34 35} When necessary, linear regression analysis will be used to evaluate correlations between values.

P values below 0.05 are considered statistically significant.

ETHICS AND DISSEMINATION

The Regional Committee for Medical Research Ethics in Norway (ID number 97615) approved the study. The trial is registered in ClinicalTrials.gov (registration date 14 October 2020). Data from the examinations will be stored in separate registration forms, where the participant is given a unique number. Thereby, data will be pseudonymous, and only the principal investigator of the study will have access to the code key. All data will be stored with restricted access.

Data collection is planned to occur from January 2022 to January 2023, the analysis of the data will presumably be finished in 2023 and manuscripts will be submitted to international peer-reviewed medical journals. Presentation of scientific abstracts at international medical conventions and oral presentations in relevant medical conventions are planned for 2023.

Both TFL and US are methods in daily use in hospitals all over the world, and both methods are considered with minimal discomfort and no risk to the patient.

DISCUSSION

We know from studies using TFL that therapies based on non-invasive application of positive/negative pressure may trigger unwanted responses from both the aryepiglottic folds and the glottic structures in healthy volunteer.⁶ To our knowledge, this will be the first study to examine feasibility and utility of laryngeal US imaging during NIV and MI-E, aiming to improve and simplify diagnostic evaluation of upper airway movements during application of these respiratory therapies. If proven feasible and accurate, laryngeal US may provide a non-invasive alternative to address upper airway patency in patients with acute or chronic respiratory failure.

The main challenge when examining the larynx with TFL during positive/negative pressure therapy is visualisation of the glottis, particularly as adduction of the aryepiglottic folds or excessive secretions sometimes compromise the view of the glottic level.⁵ Thus, using US imaging may provide a more complete view of these structures.

There are other possible structures at the supraglottic and glottic levels that can impede airflow in addition to

movement of the vocal folds and aryepiglottic folds, but the muscles that control movements of these two structures are considered essential for controlling the size of the laryngeal inlet.¹

This study compares two methods of laryngeal imaging in healthy adult participants. If proven feasible and accurate, laryngeal US should also be tested in patient populations, as it might provide a less invasive and more readily available method in diagnostics and for adjustment of treatment. In patients where TFL is not feasible due to its invasive nature, US may be a valuable alternative.

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Contributors AKB, MV, GN and TMA were responsible for the overall development of an ethically sound protocol, were involved in the conception and production of the study and the development of the initial protocol. AKB drafted the manuscript. AKB, MV, GN, TH, HHC, ODR and TMA edited drafts of the manuscript, contributed to critical revision and final approval of manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods and analysis section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by The Regional Committee for Medical Research Ethics in Norway approved this planned study with ID number 97615. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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