Airway care interventions and prone positioning in critically ill patients

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AIRWAY CARE INTERVENTIONS AND PRONE POSITIONING IN CRITICALLY ILL PATIENTS

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1 General introduction and outline of this thesis

Willemke Stilma, Louise Rose, Wilma J.M. Scholte op Reimer, Frederique Paulus and Marcus J. Schultz.

INTRODUCTION

Invasive ventilation

Each year in the Netherlands, approximately 50.000 patients are admitted to an intensive care unit to receive invasive ventilation,[1] most often because of respiratory failure that is refractory to simple oxygen supplementation.

Mucus accumulation

Invasive ventilation increases the risk of accumulation of secretions in the lower airways.[2] The relatively dry gases used for invasive ventilation cause airway mucosa to produce more mucus, often with an increased viscosity.[2] Coughing, important to clear the upper and lower airways from mucus,[2] is hampered because of the presence of the endotracheal tube. In addition, critically ill patients frequently have an impaired cough reflex or no cough reflex at all due to depressed levels of consciousness, muscle weakness, and use of sedation or muscle relaxants.

Accumulation of airway mucus can lead to the formation of atelectasis and may contribute to the development of ventilator–associated pneumonia,[3] all worsening outcome. Prevention of accumulation of airway secretions, therefore, is considered an important aspect of care for intubated patients—the effectiveness of these interventions, has not been tested too well, however.

Refractory hypoxemia

Critically ill patients may develop severe hypoxemia that is even refractory to therapy with high–flow oxygen supplementation or invasive ventilation. Rescue therapies, like ventilation with high pressures, recruitment maneuvers, and also aggressive treatments like extracorporeal life support may be needed.

Prone positioning is a relatively simple, but foremost cheap and often very effective way to improve oxygenation—despite this, prone positioning remains underused.

Airway care interventions

There are various ways to prevent mucus accumulation in invasively ventilated critically ill patients.

Airway suctioning

Mucus can be removed from the endotracheal tube, the trachea or the upper airways through 'simple' endotracheal suctioning.[4]

Artificial cough

An artificial cough can also be used. The aim of an artificial cough is to create an

upward move of mucus, from the smaller to the larger airways, where it then can be easily removed through endotracheal suctioning. With manual hyperinflation,[5] one or more large tidal volumes are given slowly by hand with a manual resuscitation bag. Then, after a short pause, the air is rapidly released from the lungs in the hope that the high expiratory flow will cause an upward mobilization of mucus. Even after extensive training and with experience this technique is applied with large and unwanted variability.[6] Mechanical insufflation–exsufflation (MI-E), a so-called 'cough assist device' may reduce this variability.[7] MI–E can mimic a cough according to predefined settings—while this certainly reduces the variability, it also reduces the direct interaction of the healthcare provider with the patient.

Heated humidification and pharmacologic interventions
Other, more preventive measures against mucus accumulation include the use of heated humidification to warm and moisten inspired air,[7] but also pharmacological strategies like preventive nebulization of mucolytics and bronchodilators. Mucolytics are used to dissolve or lower viscosity of thick mucus by breaking down the chemical bonds between molecules in the mucus.[8] Bronchodilators are usually added to prevent bronchospasms induced by the nebulized mucolytics.

Mucus classification
Currently, the choice and timing of all these airway care interventions are solely driven by clinical assessment of the amount of mucus, and also mucus viscosity. The latter is usually scored using a never validated mucus qualification score, named the 'Suzukawa scale'.[9] It may be more effective to measure mucus properties more objectively, e.g., through rheology techniques that characterize biophysical properties like the viscoelasticity.[10]

Current practice
Airway care interventions are mostly performed by ICU nurses. Since evidence for benefit of all measures described above is scarce or lacking,[5, 7, 11, 12] the practice of airway care interventions and their intensity of use may vary widely.

Prone positioning

Prone positioning improves oxygenation and also enhances mucus mobilization. Invasively ventilated patients with moderate to severe acute respiratory distress syndrome (ARDS) and refractory hypoxemia, have been shown to benefit from early prone positioning.[13]

Improving oxygenation
There are several factors that have been suggested to play a role in the benefits of prone positioning.[14] First, during prone positioning the heart is no longer causing

atelectasis because of its changed position within the thorax. Also, the chest wall compliance changes and there is a more even distribution of aeration when turning a patient prone. The latter is associated with a better ventilation–perfusion ratio. This allows changes in the ventilator setting, specifically those that are associated with ventilator-induced lung injury. Furthermore, prone positioning could reduce the afterload of the right ventricle.

Mobilization of sputum
Prone positioning could enhance mucus mobilization and evacuation since the direction of the trachea is downward. This means that gravity will now enhance a movement of mucus more cephalad towards the larger airways, instead of downwards to the smaller airways.

Practice of prone positioning
Before the coronavirus disease 2019 (COVID–19) pandemic, prone positioning remained remarkably underused in invasively ventilated patients with ARDS.[15] In the beginning of the pandemic we were uncertain whether patients with COVID–19 ARDS were to be treated alike patients with ARDS due to another cause,[16] including the use of prone positioning. Furthermore, it was unknown if patients with COVID-19 ARDS could benefit from prone positioning.

Awake prone positioning
Benefit of prone positioning may not be restricted to invasively ventilated patients—at least in theory, non-intubated patients could also benefit from prone positioning.[17, 18] The strategy of placing a non-intubated patient in a prone position is frequently called awake prone positioning. Awake prone positioning can improve oxygenation within minutes.[19] Also, since awake prone positioning, alike prone positioning of intubated patients, comes with no additional devices, it is an attractive intervention in settings with limited resources. Until the COVID–19 pandemic, awake prone positioning remained poorly used, probably because of unfamiliarity and uncertainties regarding the potential benefits and practical aspects of this intervention. Aside, it was uncertain if this strategy would improve clinical outcomes.[20]

Aims of this thesis

Studies in this thesis focus on the following two aspects of care: airway care interventions in invasively ventilated patients in general; and prone positioning in intubated and in non-intubated COVID–19 patients.

The three overarching aims of this thesis are:
1. to determine the current practice of airway care interventions in Dutch ICUs;

2. to evaluate the available evidence for benefit of MI–E in invasively ventilated patients; and
3. to study the practice of prone positioning and its association with outcomes in critically ill COVID–19 patients.

Hypothesis tested in this thesis

The three overarching hypotheses tested in the studies in this thesis are:

1. that current practice of airway care interventions in intubated critically ill patients is highly variable in the Netherlands;
2. that evidence for benefit of MI-E in invasively ventilated patients is scarce; and
3. that prone positioning improves outcome in critically ill COVID–19 patients.

Outline of the thesis

This thesis is an observational study, a national survey, a focus group study, and two secondary analyses of two nationwide observational studies.

In **Chapter 2** we discuss the routine use of airway interventions in invasively ventilated patients.

Chapter 3 reports the findings of a single center observational study named 'Airway Mucus in Invasively Ventilated Critically Ill Patients—an observational pilot study comparing rheology to a clinical classification system' (MICA). In this study we measured the rheology of 52 mucus samples in 41 invasively ventilated patients. We tested the hypothesis that airway mucus viscoelastic properties, as measured by rheology in critically ill patients receiving invasive mechanical ventilation correlates with its clinical mucus classification score. The primary outcome of this study was the correlation between the clinical mucus classification score and the viscoelastic properties of mucus. Secondary outcomes were specific viscoelastic properties.

In **Chapter 4** we report the findings of a self–administered web–based survey sent to caregivers in ICUs in the Netherlands. Our hypothesis was that current practice of, and perceptions towards airway care interventions would be highly variable due to the lack of evidence. The primary outcome was current practice of four airway care interventions. We analyzed the responses from 72 healthcare professionals, representing their ICUs.

Chapters 5 and **6** contain the study protocol and describe the findings of a scoping review. The aim of this review was to map current and emerging evidence on how MI–E is used in adult invasively ventilated critically ill patients. Based on a systematic literature search we found 28 articles to answer the answer the following questions: (1) what are clinical ICU diagnoses and/or reasons for mechanical ventilation; (2) indications and contraindications; (3) MI–E settings; (4) outcomes reported; (5) adverse events attributed to MI–E and (6) perceived barriers and facilitators for its use.

In **Chapter 7** we describe the findings of a focus group study on use of MI–E

in invasively ventilated patients. We aimed to develop in-depth understanding of factors influencing decision-making processes of healthcare professionals regarding initiation, escalation, de–escalation and discontinuation of MI–E for invasively ventilated patients including perceived barriers and facilitators to use. For the focus group study, we organized three national and one international session in which a total of 35 multidisciplinary healthcare professionals participated.

Chapter 8 reports the findings of a secondary analysis of a nationwide observational study in 734 invasively ventilated COVID-19 patients, named 'PRactice of VENTilation in COVID–19' (PRoVENT–COVID). Our aim was to study the incidence and practice of prone positioning in this cohort and to test the hypothesis that prone positioning improves the outcome of COVID-19 patients. Primary outcome was incidence and practice of prone positioning in invasively ventilated COVID-19 patients. The secondary outcome was the association of prone positioning with outcome and to determine what factors were associated with its use. We tested the hypothesis that prone positioning improves the outcome of invasively ventilated COVID-19 patients.

Chapter 9 provides a guidance for use of awake prone positioning in patients with COVID–19. The purpose of this article was to summarize evidence for benefit and to develop a set of pragmatic recommendations for awake proning in patients with COVID–19 for a better understanding and local training, focusing on settings where resources are limited. We invited an international group of 43 healthcare workers to collaborate and unite the knowledge and clinical expertise.

Chapter 10 reports on a secondary analysis of a nationwide observational prospective study in 546 patients with coronavirus disease admitted to the ICU, named the 'Practice of Adjunctive Treatments in ICU Patients with COVID-19' (PRoAcT–COVID). Our aim was to determine the practice of prone positioning in patients that did not immediately proceed with invasive ventilation after arrival in the ICU and to compare epidemiology and outcomes in patients that received prone positioning versus patients that received standard care. We hypothesized that prone positioning was used often, and that its use had associations with outcome. The primary outcome was practice of awake prone positioning in COVID–19 patients admitted to the ICU. One secondary outcome was 'treatment failure', a composite endpoint of intubation or death before day 28.

Chapter 11 summarizes the findings of the studies bundled in this thesis. In **Chapter 12** these findings are discussed in a broader context and suggestions for the future are made. **Chapter 13** contains a summary in Dutch.

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Part 1

Airway care interventions

2 Preventing mucus plugging in invasively ventilated intensive care unit patients—routine or personalized care and 'primum non nocere'

Willemke Stilma, Marcus J. Schultz, Frederique Paulus.

J Thorac Dis 2018;10:S3111-4.

We thank Dr. Rello for his comments on the results of the 'Preventive Nebulization of Mucolytic Agents and Bronchodilating Drugs in Intubated and Ventilated Intensive Care Unit Patients (NEBULAE)' study,[1] a randomized clinical trial in invasively ventilated critically ill patients that compared routine with on-demand nebulization of acetylcysteine with salbutamol with respect to duration of ventilation.[2]

Invasive ventilation increases the risk for sputum retention, since mucociliary clearance is impaired in the presence of the endotracheal tube and because relatively dry gases cause mucosa to produce more mucus. Routine airway care, consisting of repetitive endotracheal suctioning and humidification of inspired air, is thought to protect against mucus retention in the lower airways,[3,4] though robust evidence for this is largely lacking. Routine nebulization of mucolytics was thought to have additive preventive effects against sputum retention in invasively ventilated patients. The NEBULAE study, however, taught us that routine nebulizations may not be so effective, as it does not translate in shorter time spend on a ventilator.[2] We would like to echo the final line in Rello's comment that 'prevention is better than cure, but attempts at prevention must not entail other dangers'—this certainly applies for routine nebulization of mucolytics.

Ineffective coughing, resulting from depressed levels of consciousness, sedation and paralysis, together with weakness before and after extubation, is another reason why invasively ventilated patients are at increased risk for airway obstruction.[5] Cough augmentation techniques, such as 'lung volume recruitment' or 'assisted cough', are suggested to prevent respiratory complications associated with chronic conditions like neuromuscular disease.[6] With 'lung volume recruitment', also known as 'air stacking' or 'breath stacking', multiple successive insufflations result in a maximum lung volume potentially improving the strength of a natural cough.[7,8] With 'assisted cough techniques', like 'mechanical in-exsufflation' or 'cough assist' not only the tidal volume is increased, but also an inspiratory hold and a quick maximal release of air is performed, provoking an artificial cough. By creating expiratory flows higher than inspiratory flows, secretions may move cephalad.[9,10]

By now, it is increasingly suggested that the above-described techniques may also benefit patients with acute respiratory failure who need invasive ventilation. Some even suggest that these techniques should be used routinely in these patients. One recently published meta-analysis focused on the question whether cough augmentation techniques have beneficial effects in invasively ventilated critically ill patients.[11] An intensive search of the medical literature resulted in a meager number of three small investigations that studied these techniques. One trial reported a higher extubation success rate in patients that received a strategy using mechanical in-exsufflation,[12] and another trial a reduction in duration of mechanical ventilation with this intervention.[13] There were, however, several severe adverse events including secretion encumbrance with severe hypoxaemia

requiring reintubation. Other well imaginable risks like hypotension, due to the high intrathoracic pressures created with these techniques, and pneumothorax, caused by the large volumes of air in the lungs, were not reported, though maybe not collected sufficiently. These risks, for sure, are very likely to occur in critically ill patients, in whom they can also have severe consequences.

Indications for and contra-indications against cough augmentation techniques remain poorly defined. Lack of guidelines regarding indications and contra-indications, timing, machine settings, and technique to be used lead to varied use. Continuing research on this topic is eagerly awaited. Studies should not only investigate efficacy of these interventions, but also, or particularly feasibility and safety in this population of frail patients. While we think all these techniques have great potential in individual cases, we strongly argue against routine use as long as studies fail to provide robust evidence for efficacy, but certainly also for safety: 'primum non nocere'.

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3 Airway mucus in invasively ventilated critically ill patients—an observational pilot study comparing rheology to a clinical classification system

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INTRODUCTION

Critically ill patients receiving invasive mechanical ventilation are at increased risk for accumulation of secretions in the lower airways.[1, 2] Such accumulation of airway mucus can induce atelectasis and contribute to ventilator–associated pneumonia.[2] Preventive airway care interventions including humidification, endotracheal suctioning and pharmacological interventions are therefore frequently initiated during invasive ventilation.[3,4,5] However, evidence for the efficacy of these interventions is scarce and the absence of guidelines enhance variation in indications for their use.[6-8]

Currently, choice and timing of interventions is mainly driven by clinical assessment of mucus viscosity based on a mucus classification scale or preference by the treating physician.[9-11] Alternatively, airway mucus properties can be measured through rheology, a more objective parameter which characterizes its biophysical properties such as viscoelasticity.[12] Previously, studies have reported that rheology of airway secretions may help classify chronic muco-obstructive respiratory diseases and serve as a marker of disease progression.[12,13]

In this study we tested the hypothesis that airway mucus viscoelastic properties, as measured by rheology in critically ill patients receiving invasive mechanical ventilation correlates with its clinical mucus classification score.

METHODS

Study design

We performed a single–center, observational pilot study in invasively ventilated critically ill adults. The medical review board deemed this study exempt (W21_326 # 21.361). Informed consent for the use of patient data was obtained post-hoc via an opt-out system.

Patients

All subjects that were admitted to the adult Intensive Care Unit (ICU) in the Amsterdam UMC location AMC the Netherlands from September - December 2021 were screened for inclusion. Subjects with an expected duration of invasive ventilation for more than two days were eligible for participation. There were no exclusion criteria. In all subjects, passive humidification of the ventilator circuit by a heat and moisture exchanger (HME filter) was used.

Collected data

We collected baseline and demographic variables, including sex, age, respiratory comorbidities and APACHE II. Mucus was collected via a closed or open suctioning system during regular airway care by the ICU nurse at fixed time points in regular

mucus containers. Time points were (1) directly after intubation; (2) after 2 days of invasive ventilation; and (3) at extubation. Mucus samples were stored at 4°C on the ICU shortly after collection and analysed within six hours after collection.

Clinical assessment of mucus properties

Airway mucus samples were classified by the attending nurses using a previously described clinical classification system.[11] This classification system categorizes mucus into three categories: '(1) watery, defined as sputum that can be suctioned like water. After suctioning no secretions remain attached to the inner surface of the suction catheter; (2) moderate, sputum of moderate viscosity. After suctioning some secretions remain attached to the inner surface of the suction catheter; (3) tenacious, thick sputum, after suctioning most secretions are still attached to the inner surface of the suction catheter and cannot be easily removed by suctioning water through the catheter'.[11]

Rheology

The biophysical properties of mucus are involved in the mucociliary and cough clearance of secretions from the airways and can be measured by rheology. These rheological properties consist of both the viscoelastic and flow point properties of mucus. Under low shear stress, mucus is characterized by reversible deformation (energy storage); then the mucus' elasticity (G') > viscosity (G"). With increasing shear stress, mucins will align along the stress direction[12] and both elasticity and viscosity will start to decline (energy dissipation). At the flow point (i.e. critical strain and stress), viscosity overshoots elasticity and definite disruption of the mucus structure occurs. Further in-depth information about rheology and its nomenclature can also be found in this review by Lai et al.[14]

Rheological properties were determined using a dynamic, rotational rheometer (Rheomuco©). We performed strain-sweep test in oscillatory mode, at 37°C, using rough-plates to avoid slippage of the samples. The linear viscoelastic regions for elasticity (G') and viscosity (G") were calculated at a 5% strain. Flow point properties are displayed via critical strain and stress. Data quality was assessed by two independent investigators who were blinded for the mucus classification scores of samples. As per discussion with Rheonova based on unpublished findings, samples with a tan delta >0.70, thus displaying Newtonian fluid-like behaviour in the lower strain regions, were considered water-contaminated and excluded. Where possible, rheological measurements were carried out in duplicate.

Primary outcome

The primary study outcome is the correlation between the mucus classification score and the viscoelastic properties of mucus (primarily the viscoelasticity or G*). Secondary study outcomes include the viscoelastic properties at a 5% strain rate

(elasticity, G' and viscosity, G") and flow point properties (critical strain and stress) of mucus.

Statistical analysis

For the calculation of the correlation between the continuous variable viscoelasticity (G*) and the ordinal classification score of mucus a Kendall's Tau correlation coefficient was used.[15] The distribution of values classified via the clinical classification scale and the relationship between G' and G" is graphically visualized in a scatterplot. Only the mean values of rheological measurements performed in duplicate were used.

Continuous distribution of the data were assessed by visual inspection of histograms. Normally distributed variables are expressed by their mean and standard deviation (SD) or when not normally distributed as medians with interquartile ranges. Categorical variables are expressed as frequencies and percentages. Where appropriate, statistical uncertainty is expressed by the 95% confidence levels. P–values of 0.05 were used for statistical significance.

To assess the reliability of rheological measurements performed, we performed Spearman rank test as well as two-way mixed Intraclass Correlation Coefficients for absolute agreement between two duplicate measures for the log-transformed values,[12] assuming normality. All analysis are performed with the R v.4.0.3.

RESULTS

During the study period 194 eligible patients were admitted to our ICU. From these patients, 41 subjects were included in the study, from whom 52 mucus samples were collected. Six samples were excluded as they were water-contaminated or yielded too little volume. The mean age was 60.6 (SD 11.2) years, 61% was male, and comorbidity was present in the majority (n = 30, 73%) of subjects, including four subjects with chronic obstructive pulmonary disease and one with a history of asthma. Overall, the severity of illness was relatively low with a median APACHE II score of 13 [IQR 10 - 18].

Correlation between clinical mucus assessment and mucus rheology

Most samples (85%) were classified as moderately viscous by healthcare professionals, while only two (4%) samples were classified as 'watery', and three samples (6%) were classified as 'tenacious'. There was no correlation between the clinical mucus classification and the viscoelastic sputum properties, with G*: τ_b = -0.00072, p = 0,95. Similarly, there was no correlation for the clinical mucus classification and elasticity (G': τ_b = -0.00067, p = 0.95) or viscosity (G" τ_b = -0.00509, p = 0.90). The distribution of mucus classification values and G' and G" properties are displayed in **Figure 1**.

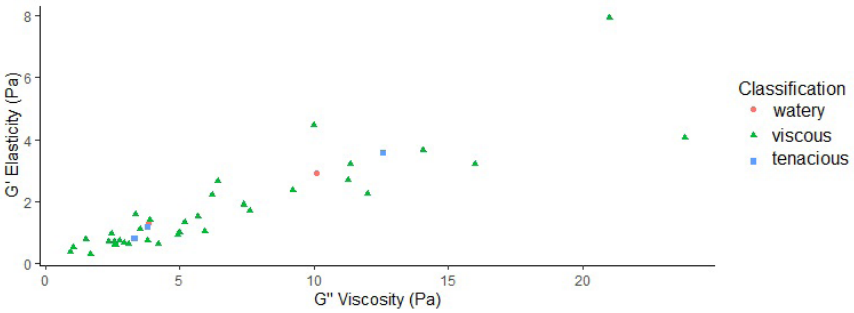

Figure 1. The distribution of mucus classification values and elasticity (G') and viscosity (G") properties.

Viscoelastic- and flow point properties of mucus in invasively ventilated patients

The mean outcomes for the viscoelastic and flow point properties are presented in **Table 1**. The reliability of duplicate measures, assessed by spearman rank tests and intraclass correlation coefficients (ICC), showed a good correlation between duplicates (n = 32, **Table 1**).

DISCUSSION

In this pilot study, we found no correlation between the clinical mucus classification and the biophysical properties of mucus as measured via rheology in critically ill subjects receiving invasive ventilation.

In this study we report on the viscoelasticity (or complex shear modulus, G*) at low strain rates, which reflects the mean mechanical impedance being the vectoral sum of the mucus' elasticity (or storage modulus, the potential of mucus to recover to its original shape after applied strain) and viscosity (or loss modulus, the tendency of mucus to flow) at that same strain rate. The viscoelasticity of airway mucus reported in this study among invasively ventilated critically ill subjects was high, occasionally even exceeding those values previously reported for mucus from spontaneous breathing CF and COPD patients.[12] Importantly, duplicate measurements had a good absolute agreement. The lack of correlation between the mucus classification scale and the viscoelastic properties of mucus may be explained as the distinction between the three categories is dominantly used for extreme values. This may lead health care professionals to classify mucus generally as moderately viscous. Importantly, the variance of viscoelasticity of the samples within this most common classification (moderately viscous) was very high, with values ranging from 1-8 Pa for G' and 1-20 Pa for G", further underscoring the lack of significant correlation.

To date, initiation of airway care interventions is based primarily on the clinical, macroscopic observations of viscous-like mucus.[9, 10] By comparing such

Table 1. Rheological properties of airway mucus in invasively ventilated patients

	Raw values	**Correlation between Duplicates & Intra Class Correlation**		
	Mean value (SD)	*Spearmans Rank (rho, p)*	*ICC (95% CI)*	*ICC interpretation**
Viscoelasticity (G*)	7.21 (5.63) Pa	r = 0.85, p < 0.001	0.781 (0.575 < ICC < 0.893)	fair -good
Elasticity (G')	6.93 (5.40) Pa	r = 0.82, p < 0.001	0.784 (0.578 < ICC < 0.895	fair -good
Viscosity (G")	1.87 (1.63) Pa	r =0.83, p < 0.001	0.784 (0.578 < ICC < 0.895)	fair - good
Damping Factor (tan δ)	0.28 (0.09)	r =0.77, p < 0.001	0.78 (0.581 < ICC < 0.891)	fair-good
Critical strain (γ_c)	20.08 (22.91)	r =0.91, p < 0.001	0.8 (0.616 < ICC < 0.902)	fair-good
Critical stress (σ_c)	35.79 (41.76) Pa	r = 0.88, p < 0.001	0.791 (0.583 < ICC < 0.9)	fair-good
Elastic force ($G^*.\sigma_c$)	338.64 (563.57) Pa^2	r = 0.88, p < 0.001	0.607 (0.313 < ICC < 0.796)	poor-good

Table legend: Spearmans Rank tests display the correlation (stability) between duplicate measures performed. Intra Class Correlation (ICC) (conform table) Interpretation ICC: < 0.50 poor, 0.50 - 0.75 fair, 0.75 - 0.90 good, 0.90 - 100 excellent.
Terminology: viscoelasticity: the mean mechanical impedance being the vectoral sum of the mucus' elasticity and viscosity. Elasticity: the storage modulus which reflects the potential of mucus to recover to its original shape after applied strain. Viscosity: the loss modulus which reflects the tendency of mucus to flow. Damping factor: the ratio of loss to storage modulus, reflects the energy dissipation of mucus. Critical strain and stress: the amount of strain or stress applied after which the mucus' viscosity overshoots elasticity due to critical breakdown of the mucus structure (crossover point). Elastic force: multiplication of the viscoelasticity of mucus and corresponding amount stress applied at the crossover point.

observations with more objective methods such as rheology measurements, our findings seriously question the use of such subjective classification scores in clinical decision-making. Currently there are no readily available, evidence-based alternatives for the classification of airway secretions to use in the clinic. In the past, the use of rheology has been hindered due to the need for specialized equipment, training and a lack of knowledge hampering data interpretation. Given the readily available samples of airway secretions in the ICU, as well as the upcoming of more user-friendly rapid rheometers, rheology might be explored as a future alternative for the classification scores in the clinic. However, much more research is needed to address whether rheology outcomes are associated with the use of mucoactive medications, course of disease or patient (sub) categories. Thereafter, and only if rheology proves to be helpful in predicting the success of interventions or outcomes in research settings, thorough clinical validation, implementation and feasibility studies should be performed before larger prospective studies may be

conducted to address the potential value of rheology as a bedside tool. This pilot study was performed to provide input for future measurements in randomized controlled trials focusing on airway care interventions in invasively ventilated patients.

This pilot study has several limitations. First, there may have been selection bias as patients were missed for sample collection and included patients had a relatively low APACHE II score.[8] Second, the number of subjects and samples were small, although in line with previous studies on airway mucus rheology.[13] As such, care should be taken not to over interpretate the results.

CONCLUSION

In this pilot study the clinical assessment of airway mucus by a clinical classification scale did not correlate with its biophysical properties as measured via rheology.

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4 Airway care interventions for invasively ventilated critically ill adults—a Dutch national survey

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ABSTRACT

Airway care interventions may prevent accumulation of airway secretions and promote their evacuation, but evidence is scarce. Interventions include heated humidification, nebulization of mucolytics and/or bronchodilators, manual hyperinflation and use of mechanical insufflation-exsufflation (MI-E). Our aim is to identify current airway care practices for invasively ventilated patients in intensive care units (ICU) in the Netherlands.

Self–administered web–based survey sent to a single pre–appointed representative of all ICUs in the Netherlands.

Response rate was 85% (72 ICUs). We found substantial heterogeneity in the intensity and combinations of airway care interventions used. Most (81%) ICUs reported using heated humidification as a routine prophylactic intervention. All (100%) responding ICUs used nebulized mucolytics and/or bronchodilators, however, only 43% ICUs reported nebulization as a routine prophylactic intervention. Most (81%) ICUs used manual hyperinflation, although only initiated with a clinical indication like difficult oxygenation. Few (22%) ICUs used MI-E for invasively ventilated patients. Use was always based on the indication of insufficient cough strength or as a continuation of home use.

In the Netherlands, use of routine prophylactic airway care interventions is common despite evidence of no benefit. There is an urgent need for evidence of benefit of these interventions to inform evidence based guidelines.

INTRODUCTION

Critically ill patients receiving invasive ventilation are at risk for retention of airway secretions.[1] The relatively dry gases used during invasive ventilation cause mucosa in the airways to produce more mucus. Moreover, the presence of the endotracheal tube hampers mucociliary clearance.[1, 2] Critically ill patients frequently have an impaired cough reflex due to depressed levels of consciousness, sedation, or muscle weakness. For these reasons, intensive care nurses apply interventions that help with evacuation of airway secretions in patients receiving invasive ventilation.

Within the domain of intensive care nursing several interventions aiming at prevention of airway secretion accumulation or promotion of airway secretion evacuation have become part of daily care for critically ill invasively ventilated patients. Active humidification i.e., use of heated humidification, helps to prevent production and thickening of airway secretions.[3] Nebulization of mucoactive agents is thought to reduce accumulation of thick and sticky airway secretions.[4] Mucoactive agents are often used in combination with bronchodilators to enhance mobilization of mucus by opening the airways.[5-7] Manual hyperinflation[8-10] or mechanical in–exsufflation (MI–E), (commonly referred to as cough assist),[8, 11, 12] may be helpful techniques in mobilizing airway secretions from smaller to larger airways, where it can be removed using suctioning. In the Netherlands, these interventions are mainly performed by intensive care nurses, involvement by physiotherapists is rare, they focus more on the traditional rehabilitation procedures. Despite common, and in some cases daily use of these airway care interventions, there is a remarkable lack of evidence for clinical benefit.[10, 12-14] Current practice guidelines[15, 16] are primarily based on expert opinion. This lack of evidence may lead to variable use of airway care interventions in daily practice based on local preferences. Our objective was to determine current airway care practices within the domain of intensive care nursing for (1) heated humidification; (2) nebulization therapy; (3) manual hyperinflation; and (4) MI-E in adult intensive care units (ICUs) in the Netherlands. A secondary objective was to investigate perceptions of safety, necessity, and efficacy of these interventions. Our hypothesis was that current practice of, and perceptions towards airway care interventions would be highly variable due to the lack of evidence.

MATERIALS AND METHODS

Study design

We used a self–report web–based cross-sectional survey design.

Survey development and formatting

The research team, with extensive experience in invasive ventilation and airway

care for critically ill patients, iteratively developed the survey. We generated potential items by searching for relevant studies in the MEDLINE and Cochrane databases. During the selection of items we focused on interventions within the domain of intensive care nursing. We did not include chest physiotherapy, like rib cage compression and other techniques aimed at flow augmentation. Previous surveys on this topic were also used to generate items.[9, 17] Item reduction occurred through discussion among the research team.

This survey comprised of 58 items, four related to ICU demographics and the remainder grouped within the airway care interventions of interest. We used skip logic when appropriate to enable provision of questions based on participant responses to preceding questions. Questions comprised intensity of use, indications and contraindications, specifics on how the intervention was applied, and how ICU team members were trained in the interventions. For MI-E, we asked additional questions on years of experience with its use in their ICU, who would prescribe and/or apply MI-E, and barriers to use. Intensity of use consisted of three categories. (1) 'Routine' defined as an intervention used prophylactically in all invasively ventilated patients and ordered with a set frequency per day; (2) 'on indication', defined as initiated based on individual patient clinical characteristics; (3) 'never', defined as never used in their ICU.

Perceptions on the safety, necessity or efficacy of airway interventions were assessed using six statements with a visual analogue scale ranging from 0 to 100 millimeters.

Survey pilot testing

The survey was loaded on to SurveyMonkeyTM[18] and was pilot tested by four ICU nurses and one intensivist from 3 different hospitals.[19] All four had experience in ICU for more than 5 years and were currently working clinically. Every pilot tester returned a checklist after testing with questions on face and construct validity including clarity, redundancy, and completeness of items, suggestions for additional items needed as well as time to complete. After pilot testing minor revisions were made, skip logic was corrected and pictures of nebulizer types were added for clarity.

Sample

Our sample comprised all adult ICUs in the Netherlands. We contacted each ICU by telephone in November 2017 to identify one senior healthcare professional who would take responsibility for survey completion on behalf of their ICU. This person was responsible for invasive ventilation policy and procedures, and either an ICU nurse, advanced ventilation nurse specialist, or physician. Advanced ventilation nurse specialists complete an additional education 14 month program on mechanical ventilation 240 study hours: 8.6 European Credit Transfer and

Accumulation System (ECTS).

Survey administration

We sent an email with instructions and the secure survey link to participants on March 2018, with 3 survey completion reminders sent over 6 weeks. Survey instructions explicitly stated the respondent was to report on current practices in their ICU (i.e., not their personal preferences). For statements regarding perceptions of the efficacy and safety of airway care interventions, we instructed respondents to provide their personal view.

Analysis plan

Frequencies and proportions were used to describe categorical data. Proportions were reported as percentages. A heat map was constructed to visualize the variability in practice of airway care interventions.[20] Airway care interventions and intensity of their use were displayed. Perceptions of respondents on statements were visualized in boxplots with means and interquartile ranges. A score of 50 was used as a threshold for agreement or disagreement. In a posthoc analysis, differences in use of airway care interventions were compared between academic-teaching hospitals and general hospitals, as well as in ICUs with ≤ 20 beds compared to > 20 beds. In addition, associations of hospital type or ICU size on the use of airway care interventions were explored by separate logistic regression models (**supplement**). Analyses were performed using SPSS (IBM SPSS Statistics 25) and R language and environment for statistical computing.[21]

Ethical considerations

The Institutional Review Board of the Amsterdam University Medical Centers, confirmed that the Medical Research Involving Humans Subjects Acts (WMO) did not apply, waiving the need for official approval (W18_024#18.035). Survey participation was voluntary and consent was implied through return of survey.

RESULTS

Participants and responses

All 85 ICUs in the Netherlands expressed interest in participation of whom 72/85 (85%) provided survey responses. Individuals responding on behalf of their ICUs were most commonly nurses (66/72, 92%); of whom 35/72 (49%) were advanced ventilation nurse specialists (**Table 1**). All ICUs were mixed medical/surgical, and both academic and non-academic hospitals were represented in the survey responses.

Table 1. Demographic characteristics of respondents and Dutch ICUs (N=72)

Characteristics	n (%)
Respondent	
ICU nurse	31 (43)
Advanced ventilation nurse specialist*	35 (49)
Intensivist	6 (8)
Hospital type	
Academic	6 (8)
Teaching†	32 (44)
General	34 (47)
ICU beds available for invasive ventilation	
3-5	10 (14)
6-10	16 (22)
11-20	20 (28)
21-30	21 (29)
>30	5 (7)

*ICU nurses with additional education 14 month program on mechanical ventilation 240 study hours;
† a non-academic hospital in which healthcare professionals are trained and educated
ICU, Intensive Care Unit

Airway care practices

Airway care intervention combinations used in each ICU are displayed as a heatmap (**Figure 1**). We found substantial heterogeneity across ICUs in intervention combinations and in the intensity of their use (i.e. routine, as indicated or never).

Heated Humidification

Most ICUs (58/72, 81%) reported prophylactic use of heated humidification as a routine intervention in all invasively ventilated patients. A minority (11/72, 15%) used heated humidification as an 'on indication' treatment, with the indication defined as presence of viscous mucus. Few (3/72, 4%) ICUs never used heated humidification.

Nebulization therapy

All responding ICUs reported using nebulization of bronchodilators and/or mucolytics. In 43% (31/72) this was as a routine prophylactic intervention for bronchospasm and mucus retention with 74% (23/31) reporting routine prophylactic nebulization therapy 4 times daily. Nine (29%) of these 31 ICUs reported more frequent administration. When used 'on indication', bronchospasm or audible wheeze were the most commonly reported indications. Bronchodilators were the most commonly used drug class, independent of intensity of use.

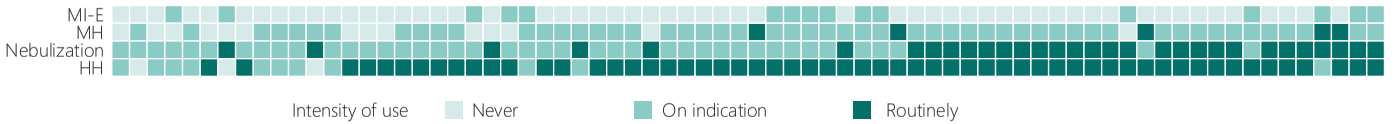

Figure 1. Heatmap airway care interventions in Dutch ICUs. Current practice of heated humidification (HH), nebulization therapy, manual hyperinflation (MH) and MI-E in Dutch ICUs is graphically displayed in a heatmap. Each vertical bar is one ICU. Intensity of use of the airway care interventions is visualized by different shadings of green according to the legend.

Table 2. Airway care interventions

Characteristics		**n (%)**	
Nebulization therapy			
Practice of use	*N=72*		
routine use		31 (43)	
as treatment on indication		41 (57)	
never used		0	
*Indications for use**		Bronchodilators	Mucolytics
bronchospasm		39 (54)	4 (6)
wheezing		37 (51)	2 (3)
in use prior to admission		29 (40)	7 (10)
decrease in tidal volume		10 (14)	2 (3)
tenacious mucus		10 (14)	33 (46)
purulent mucus		10 (14)	8 (11)
increase in peak inspiratory pressure		9 (13)	1 (1)
mucus retention		9 (13)	21 (29)
*Contra-indications**			
known drug allergy		54 (75)	
arrhythmias		23 (32)	
pulmonary edema		5 (1)	
>15 cm H_2O PEEP		4 (1)	
*Nebulizer type**			
jet nebulizer		40 (56)	
metered dose inhalers		38 (53)	
vibrating mesh nebulizer		22 (31)	
ultrasonic nebulizer		12 (17)	
Manual Hyperinflation			
Practice of use	*N=72*		
routine use		5 (7)	
as treatment on indication		53 (74)	
never used		16 (19)	
*Indications**	*N=58*		
difficult oxygenation		44 (76)	
presumed mucous presence		35 (60)	
decrease in tidal volume		28 (48)	
rising inspiratory pressures		24 (41)	
*Contraindications**			
unstable hemodynamics		35 (60)	
active pneumothorax		33 (57)	

Table 2. *Continued*

Characteristics		n (%)
intracranial hypertension		32 (55)
>15 cm H_2O PEEP		25 (43)
bronchospasm		13 (22)
pulmonary oedema		12 (20)
Materials used		
Mapleson C© (waterset) circuit		41 (71)
Laerdal AMBU© bag		10 (17)
Jackson Rees-system©		1 (2)
other †		6 (10)
Mechanical Insufflation-Exsufflation		
Practice of use	*N=72*	
routine use		0
as treatment on indication		16 (22)
never used		56 (78)
Indications *	*N=16*	
insufficient cough strength		16 (100)
already using at home		10 (63)
repeated atelectasis		8 (50)
regular airway care ineffective in removing mucus		6 (38)
prevention of reintubation		5 (31)
prevention of intubation		4 (25)
difficult weaning		3 (19)
as a weaning adjunct during all weaning		1 (6)
prevention of pneumonia		1 (6)
Contraindications *		
bullous emphysema		10 (63)
severe COPD/asthma		5 (31)
haemoptysis		6 (38)
intracranial hypertension		9 (56)
Device used		
Cough assist (Respironics (Philips)©		16 (100)
Other: IPV		3 (19)

*respondents were requested to tick all options that apply
† Mercury Medical or a combination of AMBU bag and Mapleson C waterset
Abbreviations: MV, mechanical ventilation; PEEP, Positive End Expiratory Pressure; IPV, Intra Pulmonary Ventilation; ICU Intensive Care Unit;

Metered dose inhalers (MDI) (37/72, 51%) or jet nebulizers (40/72, 56%) were most frequently used for nebulization therapy. Details on indications, contraindications and medication used are provided in **Table 2** and **Figure 1**.

Although nebulization therapy was used in all responding ICUs, perception as to efficacy (17%) or necessity (28%) of prophylactic nebulization was low. Those ICUs using nebulization as a routine prophylactic intervention, perceived efficacy to be higher than respondents from ICUs that used nebulization only on clinical indication (**Figure 2**).

Manual Hyperinflation

Most responding ICUs (58/72, 81%) reported using manual hyperinflation; most commonly (53/72, 74%) as on indication only. Those ICUs identified indications to include difficult oxygenation, presumed mucus presence, and decreased tidal volume. Unstable hemodynamics and active pneumothorax were the most important contraindications. Ten ICUs (10/58, 17%) reported to have no contraindications to manual hyperinflation.

Most ICUs reported using a Mapleson CTM circuit (41/58, 71%) for manual hyperinflation. Forty-three ICUs (74%) indicated an expiration valve was used to adjust PEEP. Twenty-five ICUs (43%) ICUs using manual hyperinflation stated a predefined PEEP target was set. Few (10/58, 17%) ICUs reported using a manometer in the circuit to measure and control for high peak airway pressures. Details on indications, contraindications and materials used for manual hyperinflation are provided in **Table 2** and **Figure 1**. Most respondents disagreed with the statement manual hyperinflation to be a safe (74%) or effective (64%) airway care intervention in invasively ventilated patients, independent of local use. (**Figure 2**).

Mechanical Insufflation-Exsufflation

Few (16/72, 21%) ICUs reported using MI-E, with use only in response to a clinical indication such as insufficient cough strength (16/16, 100%) or use of MI-E at home (10/16, 63%). MI-E was applied 2 to 3 times daily or more depending on clinical indication. Intensivists were the primary MI-E prescriber (14/16, 88%) but MI-E was applied by all ICU team members; mostly ICU nurses (15/16, 94%) and advanced ventilation nurse specialists (8/16, 50%). Years of MI-E use in the ICU setting ranged from very recent (<1 year) (3/16, 19% ICUs), 1-5 years (9/16, 56% ICUs), and 6-10 years (4/16, 25% ICUs). The majority of respondents disagreed that MI-E is a safe (75%) or effective (75%) intervention in all invasive ventilated patients, independent of local use. (**Figure 2**). Details on reported MI-E practices are provided in **Table 2** and **Figure 1**.

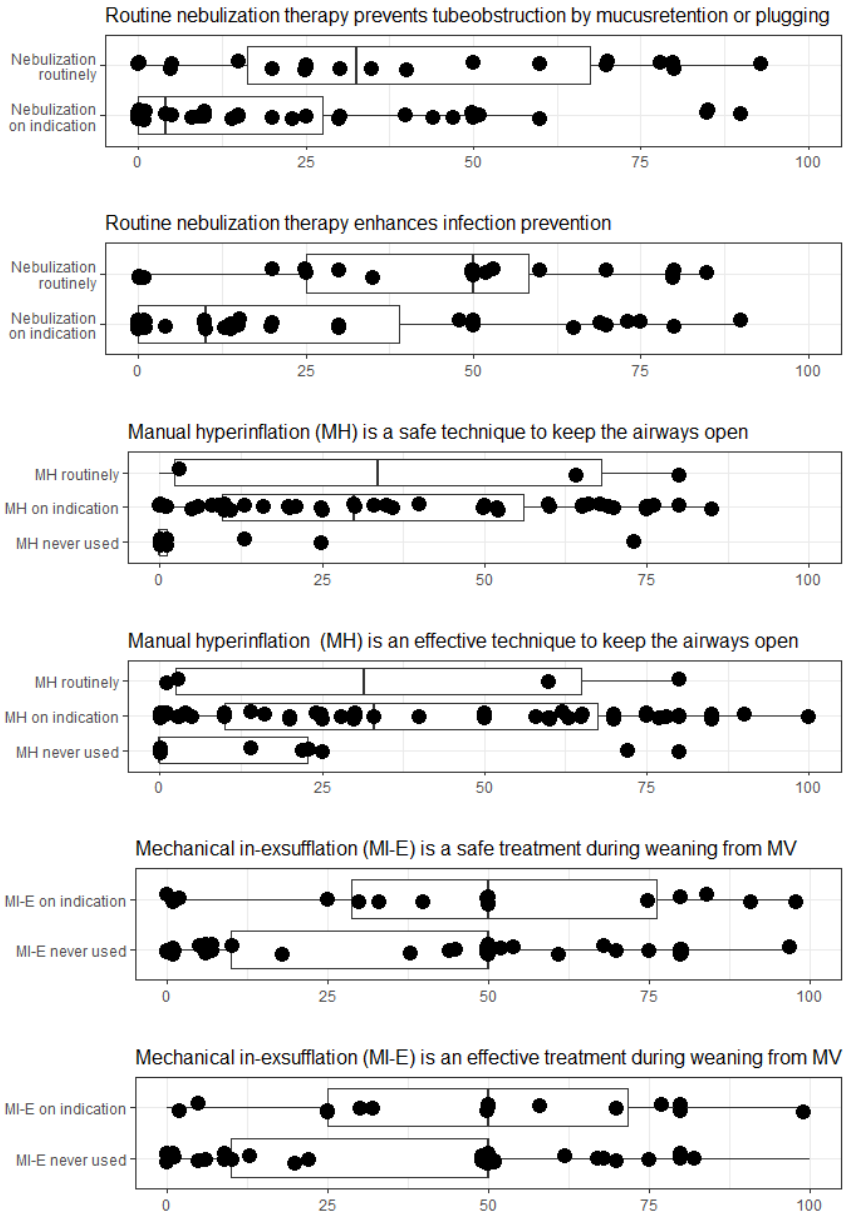

Figure 2. Perceptions of efficacy and safety of airway care interventions. Respondents could rate their perceptions on safety and efficacy of airway care interventions on a visual analogue scale from 0 (totally disagree) to 100 (totally agree). Results are grouped by reported intensity of use in their ICU.

Training and education

Most respondents described having a local protocol for nebulization therapy (57/72, 79%), manual hyperinflation (35/58, 60%) and MI-E (12/16, 75%). In 25 of the 59 (46%) ICUs that used manual hyperinflation, nurses received annual training from an expert colleague. Bedside training was the most frequently employed education method for manual hyperinflation (35/58, 60%) and MI-E (12/16, 75%).

In the post hoc analysis no differences were found in use of airway care interventions between type of hospitals or size of ICU (**Supplementary Tables S1** and **S2**). Both types of hospitals, academic-teaching and general hospitals were associated with routine use of heated humidification. The size of the ICU was not associated with its use. There were no associations of hospital type or ICU-size regarding the use of nebulization therapy. Both general and academic-teaching hospitals showed a positive association with manual hyperinflation use and ICUs > 20 beds were associated with more manual hyperinflation use. Both hospital types were associated with low use of MI-E. There was no association with size of ICU regarding MI-E (**Supplementary Table S3**).

DISCUSSION

This is the first survey describing current practice of four airway care interventions within the domain of intensive care nursing for adult patients admitted to an ICU in the Netherlands. The main findings of this survey indicate substantial heterogeneity regarding the combination of airway care interventions and their intensity of use, regardless of hospital type or ICU size. This means the type of airway care received by patients depends on where in the Netherlands they are admitted.

This survey reports a high proportion of ICUs using heated humidification as routine prophylactic therapy for all ventilated patients. This is in line with previous studies in other countries.[6, 8, 22] However, heated humidification may not only increase workload and cost,[23] but may also not be more effective compared to heat and moisture exchangers (HME) in prevention of complications. A 2017 Cochrane systematic review suggests no difference in the incidence of artificial airway occlusion, pneumonia or mortality comparing heated humidification to HME in adults and children.[13] A second systematic review in critically ill adults only, confirms these findings.[24] Our data suggest knowledge translation work is needed in the Netherlands to change airway care practice from routine prophylactic use of heated humidification in all ventilated patient to use of HMEs.

Use of routine prophylactic nebulization therapy in all ventilated patients was reported by 43% of responding ICUs. Again, evidence to support this practice is limited. This practice also increases costs and nursing workload. One multi-centre randomized controlled trial comparing routine nebulization of mucolytics and

bronchodilators with nebulization only on indication, showed no difference in the number of days alive and ventilator free.[14] In addition, medication side effects such as agitation occurred more frequently with prophylactic nebulizer use.[14]

Our results show that manual hyperinflation is commonly used in the Netherlands, both as a routine prophylactic intervention or as indicated. However, the number of ICUs reporting its use has declined since a previous survey in 2009.[9] Although alveolar recruitment and mobilization of airway secretions are cited as benefits of manual hyperinflation,[10] efficacy as a routine prophylactic intervention in all invasively ventilated patients is not confirmed by evidence.[25] Furthermore, manual hyperinflation is a difficult technique to perform and, as such, may potentially harm patient.[26] Concerns about safety of manual hyperinflation were reflected by our survey respondents.

We found use of MI-E in invasively ventilated patients uncommon in the Netherlands (21%) compared to Canada (64% of the ICUs)[17] and the United Kingdom (98% of the ICUs).[27] These surveys report MI-E to be used for invasively ventilated patients during weaning from invasive ventilation.[17, 27] There appears to be increasing adoption of MI-E for invasively ventilated patients outside the Netherlands possibly due to the need for a safe and effective way to mobilize mucus from the lower airways. However, further research is needed as to the efficacy of MI-E in invasively ventilated critically ill patients.[12]

Strength and limitations

Strength of our study is the excellent response rate meaning our data are highly generalizable to the current practice of airway care interventions of ICUs in the Netherlands. Our response rate can be attributed to following survey conduct recommendations[19] including contact by telephone prior to the survey distribution, and identification of a key respondent. Study limitations pertain to the use of a web-based self-report survey. First, by having one individual report on the practice of an ICU, responses may be reflective of perceived versus actual practice or relate to the individual's practice rather than that of the ICU. Second, the questionnaire was designed using previous reports of airway care interventions with a focus on the domain of intensive care nursing.[9, 17] Third, since we only included respondents from the Netherlands and focused on the interventions within the domain of intensive care nursing, we cannot report on other interventions applied by other health care professionals, e.g. physiotherapists. The organization of care within the intensive care differs between countries and therefore our results may be not generalizable to other countries.

CONCLUSIONS

Our survey indicates that in the Netherlands, use of prophylactic airway care interventions for heated humidification and nebulization in all invasively ventilated patients is common despite evidence of no benefit. Manual hyperinflation is frequently used, while only a minority of ICUs report to use MI-E. Substantial heterogeneity exists with regard to the combination of airway care interventions and their intensity of use. The current lack of evidence and guidelines in airway care may be a reason for the heterogeneous practices we report. There is an urgent need for evidence of benefit of these interventions, particularly when used as a routine prophylactic intervention, to inform evidence based guidelines.

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SUPPLEMENTARY APPENDIX TO CHAPTER 4

Methods posthoc analysis

Proportions and differences with 95% confidence interval of airway care interventions between type of hospitals or size of ICU were reported. To test the association of hospital type (academic/teaching compared to general hospitals) or ICU-size (> 20 beds compared to < 20 beds) with the use of heated humidification, nebulization, manual hyperinflation and mechanical insufflation-exsufflation separate logistic regression models with hospital type and ICU-size as predictors in models with the interventions as outcomes: heated humidification (on indication (1) = viscous mucus, routine (0) = always and ventilation > 24 hrs); nebulization (routine = 0 and on indication = 1); manual hyperinflation (use of MH (routine and on indication) = 1, never = 0), mechanical insufflation-exsufflation (use of MI-E (routine and on indication) = 1, never = 0). We fitted the models without an intercept to present all coefficients directly and to test the hypothesis that each individual coefficient is zero and not the pairwise comparison between coefficients. We report odds ratio's and their 95% confidence intervals).

Results posthoc analysis

Table S1. Proportions and their differences

	beds ≤ 20	beds > 20	difference
Heated humidification	0.15 (0.06 to 0.29)	0.15 (0.04 to 0.35)	0 (-0.2 to 0.16)
Nebulization	0.61 (0.45 to 0.75)	0.5 (0.3 to 0.7)	0.11 (-0.13 to 0.34)
MH	0.72 (0.57 to 0.84)	0.96 (0.8 to 1)	-0.24 (-0.4 to -0.07)
MI-E	0.24 (0.13 to 0.39)	0.19 (0.07 to 0.39)	0.05 (-0.17 to 0.23)
	Academic-teaching	**General**	**difference**
Heated humidification	0.18 (0.08 to 0.34)	0.12 (0.03 to 0.27)	0.07 (-0.11 to 0.24)
Nebulization	0.63 (0.46 to 0.78)	0.5 (0.32 to 0.68)	0.13 (-0.1 to 0.35)
MH	0.87 (0.72 to 0.96)	0.74 (0.56 to 0.87)	0.13 (-0.05 to 0.32)
MI-E	0.32 (0.18 to 0.49)	0.12 (0.03 to 0.27)	0.2 (0 to 0.38)

Table S2. Basics of the proportions

Intervention	beds ≤ 20	beds > 20
Heated humidification	7/46	4/26
Nebulization	28/46	13/26
MH	33/46	25/26
MI-E	11/46	5/26
	Academic-teaching	**General**
Heated humidification	7/38	4/34
Nebulization	24/38	17/34
MH	33/38	25/34
MI-E	12/38	4/34

Table S3. Association ICU-type and ICU-size for use of airway care interventions

Models and predictors	OR (95% CI)
Heated humidification (routine = 0; on indication = 1)	
- Academic-teaching hospital	0.23 (95% CI 0.09 to 0.48) *
- General hospital	0.13 (95% CI 0.04 to 0.34) *
> 20 ICU-beds	1.01 (95% CI 0.24 to 3.75)
Nebulization (routine = 0; on indication = 1)	
- Academic-teaching hospital	1.71 (95% CI 0.90 to 3.40)
- General hospital	1 (95% CI 0.51 to 1.97)
> 20 ICU-beds	0.64 (95% CI 0.24 to 1.7)
Manual hyperinflation (never used= 0; use of MH = 1)	
- Academic/teaching hospital	6.6 (95% CI 2.82 to 19.28) *
- General hospital	2.78 (95% CI 1.34 to 6.29) *
> 20 ICU-beds	9.85 (95% CI 1.78 to 184.82) *
Mechanical in-exsufflation MI-E (never used= 0; use of MI-E= 1,)	
- Academic/teaching hospital	0.46 (95% CI 0.22 to 0.89) *
- General hospital	0.13 (95% CI 0.04 to 0.34) *
> 20 ICU-beds	0.76 (95% CI 0.21 to 2.4)

* Significant (if the lower and upper value of the 95% confidence interval are both below or above the 1 this indicates a significant OR)

Heated humidification
Both types of hospitals, academic/teaching and general hospitals were associated with routine use of heated humidification. The size of the ICU was not associated with its use.

Nebulization therapy
There were no associations of hospital type or ICU-size regarding the use of nebulization therapy.

Manual hyperinflation
Both general and academic/teaching hospitals answers showed a positive association with manual hyperinflation use. In addition, larger ICUs were associated with more manual hyperinflation use.

MI-E
Both hospital types were associated with low use of MI-E. There was no association with size of ICU regarding MI-E.

5 The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults—a scoping review protocol

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Syst Rev 2020; 9:287

ABSTRACT

Background: Critically ill patients receiving invasive ventilation are at risk of sputum retention. Mechanical insufflation-exsufflation (MI-E) is a technique used to mobilise sputum and optimise airway clearance. Recently, interest has increased in the use of mechanical insufflation-exsufflation for invasively ventilated critically ill adults but evidence for the feasibility, safety and efficacy of this treatment is sparse.
The aim of this scoping review is to map current and emerging evidence on the feasibility, safety and efficacy of MI-E for invasively ventilated adult patients with the aim of highlighting knowledge gaps and identifying areas for future research. Specific research questions aim to identify information informing indications and contraindications to the use of MI-E in the invasively ventilated adult; MI-E settings used; outcome measures reported within studies; adverse effects reported; and perceived barriers and facilitators to using MI-E reported.

Methods: We will search electronic databases MEDLINE, EMBASE, CINAHL using the OVID platform, PROSPERO, The Cochrane Library, ISI Web of Science and the International Clinical Trials Registry Platform. Two authors will independently screen citations, extract data and evaluate risk of bias using the Mixed Methods Appraisal Tool. Studies included will present original data and describe MI-E in invasively ventilated adult patients from 1990 onwards. Our exclusion criteria are studies in a paediatric population; editorial pieces or letters and animal or bench studies. Search results will be presented in a PRISMA study flow diagram. Descriptive statistics will be used to summarize quantitative data. For qualitative data relating to barriers and facilitators, we will use content analysis and the Theoretical Domains Framework (TDF) as a conceptual framework. Additional tables and relevant figures will present data addressing our research questions.

Discussion: Our findings will enable us to map current and emerging evidence on the feasibility, safety and efficacy of MI-E for invasively ventilated critically ill adult patients. These data will provide description of how the technique is currently used, support healthcare professionals in their clinical decision making and highlight areas for future research in this important clinical area.

Systematic Review Registration: Open Science Framework submitted 9th July 2020. https://osf.io/mpksq/.

BACKGROUND

Critically ill patients under invasive ventilation are at risk for sputum retention.[1] The relatively dry gases used during invasive ventilation cause airway mucosa to produce more mucus volume, potentially of increased viscosity.[1] Cough is an important defence mechanism to clear mucus from the upper and lower airways.[1] The presence of an endotracheal tube impairs the ability to cough as the vocal cords and glottis cannot be closed. This prevents the generation of high intrathoracic pressure and subsequent enhancement of cough velocity.[2, 3] Furthermore, critically ill patients frequently have an impaired or no cough reflex due to depressed levels of consciousness, sedation, muscle weakness or muscle paralysis. Sputum retention, resulting from an inability to cough effectively, is one cause of extubation failure which in turn is associated with increased mortality.[4]

There are a number of techniques to mobilise sputum and optimise airway clearance for invasively ventilated patients. Endotracheal suctioning is the most common intervention used to remove retained airway secretions from within the endotracheal tube, trachea, and upper airways.[5] Endotracheal suctioning though is not effective for clearing secretions from the lower airways.[6]

Mechanical Insufflation-Exsufflation (MI-E) aids sputum clearance from upper and lower airways. This technique augments inspiratory and expiratory flows to improve sputum mobilisation, through the application of rapidly alternating positive and negative pressure, which approximates a normal cough.[7]

MI-E was originally developed to prevent respiratory complications associated with sputum retention for patients with neuromuscular disease.[8, 9] Recently interest has increased in the use of MI-E for invasively ventilated critically ill adults in the intensive care unit (ICU).[10] To date, evidence suggests limited and variable adoption of MI-E in this patient group. Our group has conducted practice surveys of cough augmentation techniques in ICUs in Canada,[11, 12] the United Kingdom (UK)[13] and the Netherlands.[14] Results from all surveys illustrated that MI-E was predominantly used for sputum management in non-intubated patients to prevent intubation or reintubation.[11-13] Across all three countries, MI-E was not commonly used in invasively ventilated patients. Both Canadian and UK surveys cited lack of clinician expertise and knowledge as perceived barriers to MI-E use in intubated patients.

Evidence for the feasibility, safety and efficacy of MI-E in invasively ventilated critically ill adults is sparse.[15] To date, little is known about which patients would benefit most and in which stage of mechanical ventilation i.e. before or during weaning or following extubation to prevent reintubation; the most appropriate technique or MI-E set up regarding pressure, flow, and timing of insufflation and exsufflation; incidence of adverse events; reported outcomes, as well as the barriers and facilitators for using MI-E for invasively ventilated adults in an ICU setting.

The primary aim of this scoping review is to map current and emerging

evidence on how to use MI-E for invasively ventilated adult patients with the aim of highlighting knowledge gaps and identifying areas for future research.

METHODS

Study design

Scoping review following the methods outlined by Hilary Arksey & Lisa O'Malley and advanced by other authors.[16-18]

Study questions

We will address the following study questions:

1. What primary clinical ICU diagnoses and/or reasons for mechanical ventilation are an indication to use/not use MI-E during invasive ventilation?
2. What are the clinical indications (i.e. sputum removal) and contraindications for commencing MI-E in invasively ventilated critically ill adults?
3. What MI-E settings are used for invasively ventilated critically ill adults? (i.e. interface type, flow, pressure and time settings)
4. What outcomes are reported in studies of MI-E for invasively ventilated critically ill adults and how are these outcomes measured?
5. What adverse events attributed to MI-E use are reported in the evidence base, and how are these defined/described?
6. What perceived barriers and facilitators to using MI-E for invasively ventilated critically ill adults are described in the evidence base, and how are these defined?

Identifying relevant studies

The search strategy will be developed in consultation with a medical information specialist and applied to the following bibliographic electronic databases: MEDLINE, EMBASE, CINAHL using the OVID platform. We will search PROSPERO and The Cochrane Library for relevant reviews, ISI Web of Science for conference abstracts, and the International Clinical Trials Registry Platform (apps.who.int/trialsearch) for unpublished and ongoing trials. We will screen reference lists of included articles for additional studies meeting our inclusion criteria listed below.

A modified version of the published search strategy of the Cochrane systematic review of cough augmentation techniques will be used.[15] Modification was made to solely focus on MI-E in an adult population. Additionally we will not exclude studies based on study design. The search strategy is provided in **Additional file 1**. We will not restrict article selection based on language. Inclusion and exclusion criteria are shown in **table 1**.

Table 1. Inclusion and exclusion criteria for studies

Inclusion	Exclusion
Mechanically ventilated adults via tracheostomy or endotracheal tube in a relevant clinical location (intensive care, weaning centres, respiratory high care/dependency areas)	Children (< 18 years)
Describes use of MI-E	Editorial pieces Letters to the Editor
Any study design (include randomized controlled trials (RCT), quasi and non-randomized clinical trials, before and after studies, interrupted time series cohort studies, qualitative designs, mixed methods, cross-sectional design, case reports/series, and research letters which present original data)	Bench and animal studies
Published from 1990 onwards	

Selection of studies

Two review authors (ES and WS) will independently screen titles and abstracts identified by our search methods. Full texts of studies considered by either author as potentially eligible will be obtained and reviewed to confirm selection against the inclusion/exclusion criteria. Any disagreements throughout the review process will be resolved by discussion or referred to a third reviewer for arbitration (LR/FP). Endnote x9 will be used to select articles independently.

Data charting process

The research team has developed the data charting form[17, 19] to collect information pertinent to our research questions. The data charting tool will be piloted by two authors (ES and WS) on five articles, with further refinement following discussion as required. Data will include article study demographics (author, year of publication, study location and population), study design and aim, primary clinical ICU diagnoses or reasons for mechanical ventilation of patients that use/do not use MI-E during invasive ventilation (RQ1); clinical indications and contraindications for using MI-E (RQ2); technical or practical application of MI-E (RQ3); study outcomes and measures (RQ4); adverse events/side effects (RQ5) and perceived barriers and facilitators to use of MI-E for invasively ventilated patients (RQ6).

Two reviewers (ES and WS) will independently chart these data using the data charting form. Data charting will be managed by two reviewers (WS and ES).

One reviewer will be responsible for contacting key author when clarification or additional data are needed. Contact efforts will be limited to a maximum of 3 emails.

Analysis of data

Three steps will be used to collate results.[17] Descriptive statistics will be used to summarize quantitative data. We will present counts and proportions of studies reporting each outcome that have been used by researchers. For qualitative data relating to barriers and facilitators, we will use content analysis and the Theoretical Domains Framework (TDF) as a conceptual framework.[20, 21] Finally, we will apply meaning to the results through the generation of recommendations for practice and future research based on our analyses.

Assessment of methodological quality of individual studies

Although the assessment of risk of bias is not essential for scoping reviews,[18] we will use the Mixed Methods Appraisal Tool (MMAT)[22] to give an overview of the validity of current evidence. Previous studies have shown the MMAT to be an easy to use tool with moderate to perfect inter-rater reliability.[22] Two review authors (ES/WS) will independently complete quality assessment. We will not exclude studies from the review due to determined quality. Quality assessment instead will be used to facilitate description of rigor of included studies.

Presentation of findings

We will present our search results in a PRISMA study flow diagram[18] illustrating the total number of articles generated from the search strategy and following application of the inclusion/exclusion criteria, the number subsequently excluded and ultimately used for review.

A summary table will illustrate study characteristics from included articles, including population, study country, study design and methods. Additional tables and relevant figures will present data addressing our research questions. Where qualitative data is attained tables will be produced to highlight key thematic content within each TDF domain.

Amendments

The protocol will be closely followed throughout with regular progress reports as a whole study team. If any amendments are made to the published study protocol these will be reported in the final publication.

Dissemination of findings

We plan to disseminate results from this review in a peer-reviewed journal.

DISCUSSION

There is growing interest in the role of MI-E for invasively ventilated critically ill adults but to date adoption and application of this technique is variable.[11-13] The primary aim of this scoping review is to map emerging and current evidence, on MI-E in an ICU setting, thus adding to previous Cochrane Review findings.[15] Our protocol also aims to apply the TDF framework to explore the perceived barriers and facilitators for MI-E use.[20, 21] Barriers and facilitators will be considered for the feasibility of this technique.

The results of this review will highlight gaps in the current evidence base to inform future research and will contribute to the clinical decision making processes of healthcare professionals who work with MI-E or are considering use of the technique within their ICU.

Strength and limitations

The protocol for this scoping review is transparent and in line with the PRISMA scoping review checklist[18] and the recent scoping review checklist.[23] Strengths include rigorous and systematic search, inclusion of studies in all languages, independently selection of studies, and quality assessment using the MMAT.[22]

A potential limitation is that we are focusing on a very specific patient group with an age restriction. This may restrict the amount of articles to be included.

CONCLUSION

This scoping review will provide a timely overview of emerging evidence of MI-E in invasively ventilated critically ill adults. We hope findings will facilitate clinician understanding the potential application if this technique for invasively ventilated critically ill adults and will direct future research.

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ADDITIONAL FILE 1

Search strategy for the use of mechanical insufflation-exsufflation in invasively ventilated critically ill patients: a scoping review
UPDATE: 24-2-2020 t/m 15-6-2020

15-6-2020:

Databases:			
Medline. Embase, Cinahl, Central, Web of Science	Before deduplication	After deduplication	After deduplication original document
Total	128	112	76

Searches Before deduplication:

MEDLINE (OVID):
Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to June 12, 2020
Search Strategy:

#	Searches	Results
1	(cough* adj2 assist*).ti,ab,kw.	261
2	(CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*).ti,ab,kw.	64
3	(cough* adj2 augment*).ti,ab,kw.	79
4	Cough/rh [Rehabilitation]	19
5	(in-exsufflator* or in-exsufflation*).ti,ab,kw.	44
6	(insufflat* adj1 exsufflat*).ti,ab,kw.	135
7	MI-E.ti,ab,kw.	76
8	(direct* adj2 cough*).ti,ab,kw.	60
9	(cough* adj2 flow* adj5 (improv* or increas* or enhanc* or expan* or exten*)).ti,ab,kw.	58
10	(respiratory muscle* adj2 (aid* or support*)).ti,ab,kw.	33
11	(recruit* adj2 (lung volume or aveolar)).ti,ab,kw.	116
12	((lung or alveolar) adj1 recruit* adj2 (manoeuv* or maneuv*)).ti,ab,kw.	311
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1018
14	exp Animals/ not (exp Animals/ and Humans/)	4706900
15	(comment or editorial or letter or interview or news).pt. or (letter or editorial or comment).ti. or respiratory muscle training.ti,kw.	2128982
16	13 not 14 not 15	849
17	exp Pediatrics/ or (pediatr* or paediatr* or child* or newborn* or infant*).ti.	1144485
18	(exp Child/ or exp Infant/) not exp Adult/	1662619
19	16 not 17 not 18	715
20	limit 19 to ed=20200224-20200615	19

EMBASE (OVID):
Database(s): **Embase Classic+Embase** 1947 to 2020 June 12
Search Strategy:

#	Searches	Results
1	(cough* adj2 assist*).ti,ab,kw.	492
2	(CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*).ti,ab,kw.	116
3	(cough* adj2 augment*).ti,ab,kw.	115
4	exp coughing/rh	11
5	(in-exsufflator* or in-exsufflation*).ti,ab,kw.	79
6	(insufflat* adj1 exsufflat*).ti,ab,kw.	238
7	MI-E.ti,ab,kw.	140
8	(direct* adj2 cough*).ti,ab,kw.	81
9	(cough* adj2 flow* adj5 (improv* or increas* or enhanc* or expan* or exten*)).ti,ab,kw.	89
10	(respiratory muscle* adj2 (aid* or support*)).ti,ab,kw.	57
11	(recruit* adj2 (lung volume or aveolar)).ti,ab,kw.	194
12	((lung or alveolar) adj1 recruit* adj2 (manoeuv* or maneuv*)).ti,ab,kw.	476
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1651
14	(exp animal experiment/ or exp animal model/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experiment/)	6693167
15	13 not 14	1486
16	editorial/ or letter/ or (letter or editorial or comment).ti. or respiratory muscle training.ti,kw.	1782014
17	15 not 16	1429
18	exp pediatrics/ or (pediatr* or paediatr* or child* or newborn* or infant*).ti.	1501891
19	exp child/ not exp adult/	2214791
20	17 not 18 not 19	1196
21	limit 20 to dd=20200224-20200615	26

CINAHL (EBSCO):
13 hits - Publicatiedatum: 20200201-20200631

S17	S15 NOT S16
S16	(MH "Animals+") NOT (MH "Human")
S15	S13 not S14
S14	(PT comment or editorial or letter or news) OR TI (comment or editorial or letter)
S13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S12	TI ((lung or alveolar) N1 recruit* N2 (manoeuv* ormaneuv*)) OR AB ((lung or alveolar) N1 recruit* N2 (manoeuv* or maneuv*))
S11	TI (recruit* N2 ("lung volume" or alveolar)) OR AB (recruit* N2 ("lung volume" or alveolar))

S10	TI (respiratory muscle* N2 (aid* or support*)) OR AB (respiratory muscle* N2 (aid* or support*))
S9	TI (cough* N2 flow* N5 (improv* or increas* or enhanc* or expan* or exten*)) OR AB (cough* N2 flow* N5 (improv* or increas* or enhanc* or expan* or exten*))
S8	TI direct* N2 cough* OR AB direct* N2 cough*
S7	TI "MI-E" OR AB "MI-E"
S6	TI insufflat* N1 exsufflat* OR AB insufflat* N1 exsufflat*
S5	TI ((in-exsufflator* or in-exsufflation*) OR AB ((in-exsufflator* or in-exsufflation*)
S4	(MH "Cough/RH")
S3	TI cough* N2 augment* OR AB cough* N2 augment*
S2	TI (CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*) OR AB (CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*)
S1	TI cough* N2 assist* OR AB cough* N2 assist*

Cochrane Library:

ID	Search	Hits
#1	(cough* near/2 assist*):ti,ab,kw	74
#2	(CoughAssist* or Pegaso* or Cofflator or Cof-flator* or (cough next machine*)):ti,ab,kw	26
#3	(cough* near/2 augment*):ti,ab,kw	29
#4	MeSH descriptor: [Cough] explode all trees and with qualifier(s): [rehabilitation - RH]	2
#5	(in-exsufflator* or in-exsufflation*):ti,ab,kw	20
#6	(insufflat* near/1 exsufflat*):ti,ab,kw	47
#7	(MI-E):ti,ab,kw	53
#8	(direct* near/2 cough*):ti,ab,kw	18
#9	((cough* near/2 flow* near/5 (improv* or increas* or enhanc* or expan* or exten*))):ti,ab,kw	15
#10	(((respiratory next muscle*) near/2 (aid* or support*))):ti,ab,kw	4
#11	(recruit* near/2 (lung volume or alveolar)):ti,ab,kw	501
#12	(((lung or alveolar) near/1 recruit* near/2 (manoeuv* or maneuv*))):ti,ab,kw	182
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	678
#14	(respiratory muscle training):ti,ab,kw	1831
#15	#13 not #14 666	
#16	(pediatr* or paediatr* or child* or newborn* or infant*):ti	100349
#17	#15 not #16	579
#18	MeSH descriptor: [Pediatrics] explode all trees	659
#19	#17 not #18 with Cochrane Library publication date Between Feb 2020 and Jun 2020, in Cochrane Reviews, Trials	26

WEB OF SCIENCE:
44 hits
Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.
TOPIC: ((((cough* NEAR/2 assist*)) OR ((CoughAssist* or Pegaso* or Cofflator* or Cof-flator* or cough machine*)) OR ((cough* NEAR/2 augment*)) OR (("in-exsufflator" or "in-exsufflators" or "in-exsufflation" or "in-exsufflations")) OR ((insufflat* NEAR/1 exsufflat*)) OR ("MI-E") OR ((direct* NEAR/2 cough*)) OR ((cough* NEAR/2 flow* NEAR/5 (improv* or increas* or enhanc* or expan* or exten*))) OR (((("respiratory muscle" or "respiratory muscles") NEAR/2 (aid* or support*))) OR ((recruit* NEAR/2 ("lung volume" or alveolar))) OR (((lung or alveolar) near/1 recruit* near/2 (manoeuv* or maneuv*))))) NOT TOPIC: (respiratory muscle training) NOT TITLE: (pediatr* or paediatr* or child* or newborn* or infant*) NOT TOPIC: ((animals NOT humans)) NOT DOCUMENT TYPES: (Bibliography OR Correction OR Correction, Addition OR Discussion OR Editorial Material OR Letter OR Meeting Abstract OR News Item OR Note)
Refined by: PUBLICATION YEARS: (2020)
Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years

6 The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults—a scoping review

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ABSTRACT

Mechanical insufflation-exsufflation (MI-E) is traditionally used in the neuromuscular population. There is growing interest of MI-E use in invasively ventilated critically ill adults. We aimed to map current evidence on MI-E use in invasively ventilated criticall ill adults. Two authors independently searched electronic databases MEDLINE, Embase and CINAHL via the OVID platform, PROSPERO, The Cochrane Library, ISI Web of Science and International Clinical Trials Registry Platform between January 1990 and April 2021. Inclusion criteria were (1) adult critically ill invasively ventilated patients, (2) use of MI-E, (3) study design with original data, (4) published from 1990 onwards. Data were extracted by two authors independently using a bespoke extraction form. We used Mixed Methods Assessment Tool to appraise risk of bias. Theoretical Domains Framework was used to interpret qualitative data. Of 3090 citations identified, 28 citations were taken forward for data extraction. Main indications for MI-E use during invasive mechanical ventilation were presence of secretions and mucus plugging (13/28, 46%). Perceived contraindications related to use of high levels of positive pressure (19/28, 68%). Protocolised MI-E settings with a pressure of +/- 40 cm H_2O were most commonly used with detail on timing, flow and frequency of prescription infrequently reported. Various outcomes were reintubation rate, wet sputum weight, and pulmonary mechanics. Only 3 studies reported the occurrence of adverse events. From qualitative data, the main barrier to MI-E use in this patient group was lack of knowledge and skills. We concluded that there is little consistency in how MI-E is used and reported and therefore recommendations about best practices are not possible.

INTRODUCTION

Cough is an essential defence mechanism in clearing mucus from the airways. In invasively ventilated patients, cough is impaired due to an artificial airway as the vocal cords and glottis remain abducted.[1, 2] Sedation further exacerbates sputum retention as it limits the cough reflex, mucociliary clearance and muscle strength. As a result, sputum retention in patients with an advanced airway is a common problem that may have substantial impact on ability to wean and to be extubated in the longer term.[3]

Airway clearance techniques are used by clinicians to mobilise and clear retained secretions. Endotracheal suctioning is most commonly used to remove secretions from the endotracheal tube, tracheostomy and the upper airway.[4] However, limitations to this technique include the inability to clear secretions from the lower airways and potential trauma to the upper airways.[2]

Mechanical insufflation-exsufflation (MI-E) is traditionally used in the neuromuscular population.[5-7] It is conventionally used as a non-invasive device that delivers a positive pressure breath to optimise tidal volume (VT) and lung recruitment, and then quickly alternates to a negative pressure breath. It is this rapid alternation between positive and negative pressure breaths that augments gas flow rates, improves sputum mobilisation, and ultimately stimulates a cough.[6] More recently, there has been growing interest of MI-E use for intubated critically ill adults.[7] Our research group has completed a number of practice surveys in Canada,[8, 9] the Netherlands[10] and the United Kingdom.[11] These surveys illustrate the variable adoption of MI-E both nationally and internationally. Barriers to use cited in these surveys include limited clinician experience and knowledge of MI-E. Additionally, results illustrated MI-E use predominantly in the non-intubated critically ill patient group.[8, 9, 11] The most frequently cited indication for MI-E use was the optimisation of sputum clearance to prevent intubation or re-intubation.[8-11] A Cochrane systematic review concluded that further research is required to establish the feasibility, efficacy and safety of MI-E in the intubated population given the dearth of efficacy studies.[12]

The aim of this scoping review was to map current and emerging evidence on how MI-E is used in invasively ventilated critically ill adults. We sought specific detail regarding the patient groups and stage of mechanical ventilation for which MI-E as well as the practical application including pressures, times and flow rates. We also sought to describe the outcomes and measures reported in MI-E studies as well as adverse events. This information will be used to inform research design in future MI-E studies.

METHODS

Study design

This scoping review followed the methods outlined by Arksey and O'Malley and advanced by other authors.[13-15] The scoping review protocol has been previously published.[16] There were no amendments made to the protocol during the conduct of the scoping review.

Study identification

Our search strategy was a modified version of that previously used for the Cochrane systematic review of cough augmentation techniques in the critically ill.[12] Modification required removal of terms used for airway clearance strategies other than MI-E. Furthermore, we did not exclude studies based on study design and did not restrict article selection based on language.[16]

The search criteria were applied between January 1990 and April 2021 using electronic databases MEDLINE, Embase and CINAHL via the OVID platform. PROSPERO and Cochrane Library were searched for relevant reviews, ISI Web of Science for conference abstracts and the International Clinical Trials Registry Platform (apps.who.int/trialsearch *Accessed April 12, 2022*) for unpublished and ongoing trials. The reference lists of relevant studies and reviews were examined to highlight any additional articles for inclusion.

Study selection and data extraction

Criteria for inclusion of articles were (1) adult population with invasive mechanical ventilation via endotracheal tube or cuffed tracheostomy in an intensive care setting, (2) use of MI-E, (3) any study design with original data, (4) published from 1990 onward. Citations were excluded if they included participants < 18 years or if they were editorial pieces, letters to the Editor, bench or animal-based studies.

Screening and data extraction was performed by two review authors (ES and WS) independently using a piloted data extraction form. Reviewers were responsible for contacting key authors for clarification of methods or additional data, if required. Any disagreements during the review process were recorded and resolved by discussion or referred to a third reviewer (LR) for arbitration. EndNote x9 (Clarivate, Philadelphia, Pennsylvania) was used to manage citations.

Methodological Quality Assessment

The Mixed Methods Assessment Tool[17] was used to provide an assessment of study quality of full text papers. Quality scores were not used to exclude studies. Citations of full publications only were scored by assigning quality scores 0 - 100% (0% 'no criteria met' - 100% 'all criteria met') with 20% assigned per methodological criteria of which there were five per study design. Score ratings > 80% were classified

as high quality, 80% moderate quality and < 80% low quality.[17] This process was completed independently by the reviewers (ES and WS) and then compared and discussed to generate consensus on ratings.

Data analysis

Descriptive statistics were used to summarise quantitative data. The Theoretical Domains Framework[18, 19] was used to interpret qualitative data relating to barriers and facilitators of MI-E use in invasively ventilated critically ill adults.

RESULTS

The initial search generated 3,090 unique citations. The full text papers of 133 citations were assessed for eligibility. Once inclusion and exclusion criteria were applied, 34 citations representing 28 studies were taken forward for data extraction. One conference abstract was additionally highlighted through direct contact with an author. The search results are presented using a PRISMA study flow diagram (**Figure 1**).

Most studies (no. = 9) were randomised controlled trials (5 full-text publications[20-24], 3 trial registrations[25-27] and one abstract[28]) or descriptive studies (no. = 19) including observational cohort studies (no. = 7)[29-35], surveys (no. = 6)[8, 10, 11, 36-38] and case study/series reports (no. = 5)[39-43] and a cross-over trial (no. = 2).[25, 44] Studies were completed in 13 different countries. The Mixed Methods Assessment Tool was completed for the 19 full-text publications. Only 5/19 (26%) studies scored 100% (high quality).[8, 10, 11, 23, 29] (**Table 1** and **appendix 1**, see related supplementary materials at http://www.rc.rcjournal.com).

Population

Of the 28 studies, 20 studies provided information on the ICU population in which MI-E was studied (trial registrations no. = 3 and survey data no. = 5 excluded). Studies varied in terms of subject population with dissimilar reasons for intubation/invasive ventilation. The primary reason for intubation was recorded in 17/20 (85%) and was most commonly acute respiratory failure (no. = 12). Multiple underlying causes of acute respiratory failure were stated across studies including post-operative respiratory failure; pneumonia; cardiac arrest, acute spinal cord injury and neuromuscular disease (NMD). Duration of mechanical ventilation ranged from a minimum of 24 hours to 10 days at the time of recruitment (**Table 1**).

Clinical indications and contraindications

We identified 10 different indications for use of MI-E. In clinical studies the most commonly reported indication was presence of secretions and mucus plugging (9/28, 32%), followed by prophylactic airway clearance (7/28, 25%).

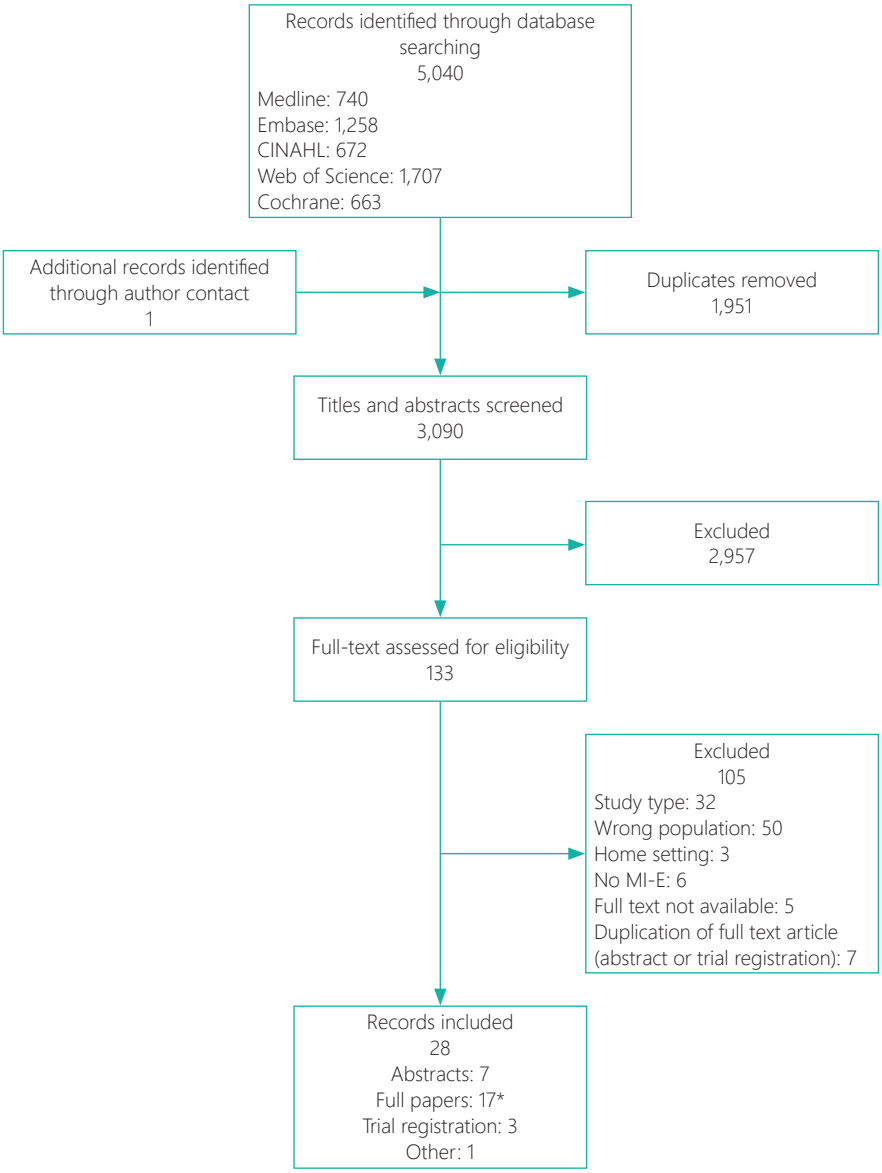

Figure 1. PRISMA Flow chart.
* Full paper identified of 2 abstracts after closing the search.

Table 1. Study characteristics

Author, year	Citation format	Country	N	Population description	Primary ICU diagnoses /reason for MV	Interface	Outcomes	MMAT (%)
Randomised controlled trials								
Goncalves, 2012[22]	Full paper	Portugal	75	General ICU	Acute hypoxaemic and/or hypercapnic RF from a specific etiology	ETT	Re-intubation; mortality; total ICU LOS; post extubation LOS; NIV failure rates	80
Coutinho, 2018[21]	Full paper	Brazil	43	Invasive ventilation > 48 hours	Traumatic brain injury; post-operative; polytrauma	-	Secretion clearance; haemodynamics (heart rate, systolic and diastolic blood pressure, Mean Airway Pressure); respiratory mechanics (VT, MV, RR, Crs, Rrs); SpO_2	80
Ferreira de Camillis, 2018[23]	Full paper	Brazil	180	Invasive ventilation >24 hours	Acute RF, decreased level of consciousness, hemodynamic stability, postop, cardiac arrest	ETT	Wet aspirated sputum weight; Crs; Rrs, work of breathing; adverse ventilator or hemodynamic event	100
Campos, 2019[20]	Full paper	Brazil	22	Invasive ventilation >10 days; no VAP	Post-operative RF (retained secretions)	ETT	VAP incidence, MV duration, ICU LOS, mortality, bronchoscopy use, antibiotic use, bronchial obstruction	60
Jprn, 2018[26]	Trial registration	Japan	-	Invasive ventilation in ICU >24 hours and expected for 48 hours	-	-	Ventilator days; ICU days; reintubation; tracheostomy	-
NCT04149873, 2019[27]	Trial registration	Taiwan	240*	Invasive ventilation on Pressure Support mode	Post operative	ETT	Re-intubation rate, ICU mortality, post extubation LOS	-

Table 1. *Continued*

Author, year	Citation format	Country	N	Population description	Primary ICU diagnoses /reason for MV	Interface	Outcomes	MMAT (%)
Sanchez Garcia, 2019[28]	Abstract	Spain	120	Critically ill patients	-	ETT or TT	Safety, tolerance (pain and agitation scores, sedation/responsiveness score)	80
Martínez-Alejos, 2021[24]	Full paper	France, Spain	26	Invasive ventilation >48 hours	-	ETT	Sputum volume; effects on respiratory mechanics, hemodynamics and safety	100
Observational Cohort								
Bach, 2010[29]	Full paper	USA, Portugal	157	NMD, Critical Care Myopathy	Acute RF due to pneumonia and/or surgery	ETT	Successful extubation; Vital Capacity, duration on NIV, CPF, pre-intubation NIV experience; total days intubated	100
Soares, 2014[35]	Abstract	Portugal	27	NMD	NMD with respiratory failure	TT	CPF	
Bach, 2015[32]	Full paper	USA	98	NMD with previous failed extubations	RF (pneumonia)	ETT	Successful extubation; SpO_2; CPF; Vital Capacity	80
Farina, 2017[33]	Abstract	Spain	13	-	-	ETT and TT	Sputum clearance; ventilator/lab/ respiratory parameters	
Sánchez García, 2018[31]	Full paper	Spain	13	Invasive ventilation patients	Peritonitis, severe pancreatitis, nosocomial pneumonia, RF, coma, severe Community Acquired Pneumonia, bronchospasm, cardiac arrest	ETT and TT	Ventilator modes and parameters, arterial blood gas, hemodynamic parameters, adverse events; secretion clearance; device tolerance	80

Kikuchi, 2019[30]	Full paper	Japan	10	NMD hospitalised with routine MI-E >1 year	acute RF	TT	CPF	80
Kuroiwa, 2021[34]	Full paper	India	30	Invasive ventilation patients	RF-medical, post-operative, trauma	ETT and TT	VAP incidence; MV duration, LOS ICU, mortality, no of VAP/MV duration; bronchoscopy frequency, bronchoscopy/MV duration; antibiotic use; antibiotic/MV duration; bronchial obstructions	80
Crossover study								
ISRCTN25106564, 2013[25]	Trial registration	France	-	Invasive ventilation <7 days and expected for >48 hours	Acute RF	ETT	Secretion drainage procedures 24hrs AND secretion volume; VAP incidence; extubation failure; hospital & ICU LOS, ICU & hospital mortality	-
Sancho, 2003[44]	Full paper	Spain	6	ALS	Respiratory tract infections	TT	SpO_2, Peak Inspiratory Pressure, Mean Airway Pressure, work of breathing; wet sputum weight and volume; patient preference for comfort and effectiveness	80
Case study/series report								
Bialais, 2010[39]	Full paper	Belgium	1	Post operative	RF-atelectasis	ETT	Atelectasis resolution	20
Khan, 2015[42]	Abstract	USA	5	ALS	Emergency intubation due to respiratory failure	ETT	Extubation success; interventions used; respiratory muscle strength; bulbar function; cough strength; ICU LOS; hospital LOS; survival; discharge location	-
Tan, 2017[40]	Full paper	Malaysia	2	Acute spinal cord injury	Post operative prolonged weaning and prolonged weaning post cervical SCI	ETT and TT	CPF	80

Table 1. *Continued*

Author, year	Citation format	Country	N	Population description	Primary ICU diagnoses /reason for MV	Interface	Outcomes	MMAT (%)
Vokes, 2019[41]	Abstract	UK	1	Previously fit and well	Aspiration pneumonia	ETT	Secretion clearance; FiO_2; arterial blood gas	-
Guarnieri 2020[43]	Abstract	Italy	23	Cervical SCI	RF	ETT and TT	Extubation failure	-
Surveys								
Schmitt, 2007[36]	Full paper	USA	86	SCI	-	-	Device use, patient satisfaction	60
Prevost, 2015[37]	Full paper	Canada	114	Respiratory therapists	NMD, SCI	-	Device use	80
Rose, 2016[8]	Full paper	Canada	157	ICU clinicians	-	-	Device use	100
Garstang, 2000[38]	Full paper	USA	18	traumatic SCI	RF	TT	Patient's experience/preference (pain, preference, fatigue)	60
Stilma, 2019[10]	Full paper	Nether-lands	78	ICU professional with expertise in airway care	NA	-	Device use	100
Swingwood, 2019[11]	Full paper	UK	166	ICU Physiotherapists	NA	-	Device use	100

Cyn. = 30
*Sample size mentioned in trial registration
Abbreviations:
CPF, Cough Peak Flow; Crs, lung compliance; ETT, endotracheal tube; LOS, length of stay; MMAT, Mixed Methods Appraisal Tool, MV, mechanical ventilation; N, number of participants; NIV, non-invasive ventilation; NMD, Neuromuscular disease; NIV, non-invasive ventilation; RF, respiratory failure; Rrs, Airway Resistance; SCI, Spinal Cord Injury; TT, Tracheostomy Tube; UK, United Kingdom, USA, United States of America; VAP, ventilator acquired pneumonia; - or NA, not stated/ applicable

Contraindications relating to concerns about using high levels of positive pressure (9/28, 32%) were most common. These findings were mirrored in survey reports of healthcare professionals. (**Table 2**).

Table 2. Reported indications and contraindications MI-E

	Clinical studies No. (%)	**Survey studies in healthcare professionals**
Indications	***No. (%)***	***No. (%)***
Secretions and mucus plugging	9 (32)	4 (14)
Prophylactic airway clearance	7 (25)	
Reduced cough peak flow or insufficient cough	4 (14)	2 (7)
NMD or SCI		4 (14)
Previous domiciliary use		2 (7)
Weaning failure	4 (14)	2 (7)
Atelectasis	3 (11)	2 (7)
Respiratory failure	2 (7)	2 (7)
ICU aquired weakness		1 (3)
Need for endotracheal suctioning	3 (11)	
Contraindications		
Contraindications to increased positive pressure[†]	9 (32)	9 (30)
Recent surgery (pulmonary/thoracic/abdominal/neuro)	3 (11)	4 (14)
Mechanical ventilation settings (FiO_2 > 60% or PEEP >10 mmHg or Ppeak >40 mmHg)	2 (7)	1 (3)
(Severe) bronchospasm, COPD or asthma	1 (3)	
Hemodynamic instability	1 (3)	1 (3)
Active tuberculosis	1 (3)	
Increased intracranial pressures (>25 mmHg)		2 (7)
Severe COPD or asthma		2 (7)
Impaired consciousness (inability to respond to direct simple commands)		1 (3)
Trauma (facial, cranial, rib fractures)		1 (3)
Other[‡]	6 (21)	

no. = 28*
*Multiple indications/contraindications per study.
[†] These included pneumothorax, hemothorax, hemoptysis, emphysema, subcutaneous emphysema, pulmonary bullae, barotrauma.
[‡] Other: palliative care, hemofiltration via jugular catheter, pregnancy, strict dorsal position, contractures, nausea and vomiting.
Ppeak = peak pressure

Clinical studies

All 20 clinical studies reported on one or more elements of MI-E device settings. A range of devices were used; 11 (55%) reported using the E70 device (Philips Respironics, Carlsbad, CA, USA) and 2 (10%) the Emerson Cough Assist device (Emerson Cough Assist, Cambridge, MA). Eleven clinical studies did not specify device used. Twelve (60%) studies reported use via an endotracheal tube, 4 (20%) via tracheostomy, and 6 (40%) via a combination of endotracheal tube and tracheostomy.

A pressure setting combination of ± 40 cm H_2O was most commonly used across reporting studies (10/20, 50%).[21-24, 26, 28-30, 39, 44] Time settings were reported in 11/20 (55%) studies.[21-24, 29, 30, 34, 39-41, 44] Most commonly used time settings were inspiratory time 3 seconds; expiratory time 2 seconds and pause 1 second. A pause duration was reported in 8/20 (40%) studies.[20-24, 30, 34, 44] Five studies (25%) reported use of one insufflation prior to an exsufflation breath (not reported in the remaining studies). Flow profile was specified in only 3 (15%) studies and was set at medium (no. = 2)[20, 28] or high (no. = 1).[31] Use of oscillation was reported in 5/20 (25%) studies with 3/5[20, 28, 33] applying this option. One study applied an oscillation amplitude of 10 and frequency of 20 Hz,[20] whereas only oscillation frequency was reported in the remaining two studies as 'high'[33] or 16 Hz. Treatment regimes varied across studies with MI-E cycles being repeated up to every 20 minutes;[29] hourly;[32] 1-2 times per day;[34] 3 times a day,[22] 4 times a day[43] and most commonly up to once per day.[20, 21, 23, 24, 30, 31, 33, 39, 44] Five studies (25%) reported the inclusion of other treatment adjuncts along-side MI-E including side positioning,[43] manual assisted cough[34] and suction.[24, 41, 44] **Table 3** provides an overview of described settings of MI-E use in invasively ventilated critically ill patients.

Seven (25%) studies described the individual applying MI-E. This was most commonly physiotherapists or respiratory therapists,[22, 23, 30, 34, 41] followed by ICU nurses,[22, 29] caregivers/family[29, 32] and ICU physicians.[22]

Outcomes and measures

Of the 28 studies, 23 were appropriate to extract outcomes and measures, the remaining 5 were survey-based studies reporting on organization of care.

We identified 21 different outcomes measured in included studies (**Table 4**). Only 7 studies (7/23, 30%) clearly specified a primary outcome; these included aspirated/wet sputum weight;[23, 24] re-intubation rate;[22] suction frequency;[25] number of ventilator/ICU days,[26] incidence of ventilator associated pneumonia (VAP)[34] and mortality rate in 1 year.[27]

Five (5/23, 22%) studies reported on one outcome only. These included cough peak flow (no. = 3);[30, 35, 40] re-intubation rate (no. = 1),[43] atelectasis resolution (no. = 1).[39] Pulmonary mechanics was the most frequently reported outcome overall (no. = 9).[21, 23, 24, 29, 31-33, 42, 44] These measurements encompassed measures of tidal

Table 3. Detailed overview of MI-E settings across studies

Author (year)	Mode	Insufflation pressure (cmH_2O)	Exsufflation pressure (cmH_2O)	Insuff time (sec)	Exsuff time (sec)	pause (sec)	flow profile	Insuff repeat	Treatment regime
Randomised controlled trials									
Goncalves, 2012[22]	-	40	40	3	2	3	-	1	8 cycles* per session, 3 sessions per day. 1 day whilst intubated, 2 days post extubation
Coutinho, 2018[21]	auto timed	40	40	3	3	0	-	1	5 repetitions of 4 cycles
Ferreira de Camillis, 2018[23]	-	40	40	2	3	2	-	-	3 repetitions of 10 cycles
Campos, 2019[20]	-	30	15	2	2	0.5	medium	-	30 seconds on, 30 seconds off until 5 minutes
Jprn, 2018[26]	-	40	40	-	-	-	-	-	10 cycles
Sanchez Garcia, 2019[28]	-	50	50	-	-	-	-	-	-
Martínez-Alejos, 2021[24]	automatic	40	40	3	2	1	medium	-	4 repetitions of 5 cycles, with 1 minute rest between repetitions
Observational Cohort									
Bach, 2010[29]	manual	40	40	-	-	-	-	-	Up to every 20 minutes to maintain or return pulse oxygen saturation to >95% in ambient air
Soares, 2014[35]	-	30-70	30-70	-	-	-	-	-	-
Bach, 2015[32]	manual	60-70	60-70	-	-	-	-	-	hourly while awake
Farina, 2017[33]	-	50	45	3	4	-	-	-	2 cycles per session
Sánchez García, 2018[31]	patient triggered	50	45	3	4	-	high	1	2 repetitions of 10-12 cycles

Table 3. *Continued*

Author (year)	Mode	Insufflation pressure (cmH_2O)	Exsufflation pressure (cmH_2O)	Insuff time (sec)	Exsuff time (sec)	pause (sec)	flow profile	Insuff repeat	Treatment regime
Kikuchi, 2019[30]	automatic	40	40	1.5	1.5	2	-	0	2 repetitions per cycle
Kuroiwa, 2021[34]	-	15-40 (started low and gradually increased, through auscultation and changes in SpO_2)	15-40	2-3	2-3	2	-	-	2 repetitions of 5-10 cycles
Crossover									
ISRCTN25106564, 2013[25]	-	-	-	-	-	-	-	-	daily intervention until day 14 or extubation
Sancho, 2003[44]	-	40	40	2	3	1	-	-	5 cycles
Case study/series report									
Bialais, 2010[39]	manual	40	40	-	-	-	-	-	10 repetitions of 5 cycles
Tan, 2017[40]	-	25 building up to 40 in increments of 50	26 building up to 40 in increments of 40	-	-	-	-	-	6-10 cycles with 20-60sec rest between each cycle
Vokes, 2019[41]	-	40	45	-	-	-	-	-	-
Guarnieri 2020[43]	-	-	-	-	-	-	-	-	4 times a day

Abbreviations: -, data not supplied
*cycle refers to an insufflation breath rapidly followed by an exsufflation breath

Table 4. Outcomes measured*

Outcomes	Frequency
Physiologic variables	
Pulmonary mechanics	9 (39)
Extubation failure/success	8 (35)
Secretion clearance/wet sputum weight	7 (30)
Cough peak flow	5 (22)
Pain/agitation score	5 (22)
Adverse event	5 (22)
Device use	3 (13)
Ventilator Acquired Pneumonia incidence	3 (13)
Patient preference	3 (13)
SpO_2	2 (9)
Bronchoscopy use	2 (9)
Antibiotic use	2 (9)
Frequency of bronchial obstructions	2 (9)
Haemodynamic parameters	2 (9)
Work of breathing	2 (9)
Atelectasis resolution	1 (5)
Clinical outcome	
Mechanical Ventilation duration	4 (17)
Non Invasive Ventilation failure rate	3 (13)
ICU length of stay	7 (30)
Mortality	5 (22)
Discharge location	1 (4)

Data are shown as no. (%)
*multiple outcomes reported per study at times

volume, minute ventilation, airway resistance, lung compliance and vital capacity. Eight studies (8/23, 35%) reported on extubation failure/success;[22, 25-27, 29, 32, 42, 43] seven studies (7/23, 30%) reported on secretion clearance or wet sputum weight.[21, 23-25, 31, 33, 44] Methods of outcome measurement varied across studies. Secretion clearance was primarily measured by aspirated sputum or sputum weight, most commonly at 5 minutes post study intervention.[23, 44] When needed, 10 ml NaCl was used to rinse the suction catheter and that weight was extracted from the result.[23] Alternatively, secretion clearance was measured by frequency of endotracheal suctioning over a 24-hour period.[25] Ventilator associated pneumonia incidence was measured throughout the period of intubation, with the frequency of assessment being unclear.[20, 25, 34] The definition of ventilator associated pneumonia provided was 'pneumonia in a patient who was on mechanical ventilation for > 48 hours'.[34]

Re-intubation rate or extubation failure was used as an outcome measure in 8 (8/23, 35%) studies and defined in 3/8 studies. Definitions of extubation failure varied across studies including '48 hours following extubation';[22] 'not needing a tracheostomy during hospitalisation or at any time during follow-up'[32] and 'discharge without re-intubation'.[29]

Timepoints for measuring pulmonary mechanics were 5 minutes before and after the intervention, and 1 hour after the intervention. Cough peak flow was measured during and after intubation, mostly using the MI-E device.[30, 35, 40]

Adverse events

Adverse events were addressed in 13/20 (65%) studies. For reporting purposes, we grouped adverse events into 3 commonly occurring categories, namely 'respiratory', 'hemodynamic' and 'other' (**Table 5**).

Of the 13 studies, 10 studies reported no occurrence of adverse events in relation to MI-E. Three studies did report on the occurrence of adverse events.[8, 24, 42] Documented adverse events included oxygen desaturation (< 85%),[24] haemodynamic variation (increase or decrease of heart rate or blood pressure for > 15-20% from baseline),[8, 24] re-intubation,[42] pneumothorax,[8, 42] mucus plugging,[8] haemoptysis,[8] chest pain.[8]

Barriers and facilitators to MI-E use

We found no qualitative studies to include in the scoping review, however three survey studies reported qualitative data from open-ended questions.[8, 11, 36] Themes illustrating barriers and facilitators to MI-E use were grouped under 6 of the 14 Theoretical Domains Framework domains; knowledge, skills, beliefs about consequences, intention, environmental context and resources, and social influences (**Table 6**). Barriers to MI-E use in the critically ill included the impact of team culture, a lack of clinical experience, and the need for additional resources and training with the device. Conversely, data illustrated positive intention to use the device with this patient group, with positive experiences described to date.

DISCUSSION

In this scoping review we mapped current and emerging evidence on MI-E use in invasively ventilated critically ill adults. We included 25 completed studies and 3 trial registrations published between January 1990-April 2021. Findings show that MI-E is predominantly used in ICU patients who have difficulties in weaning and sputum clearance. Studies predominantly investigated MI-E use in patients with NMD and acute spinal cord injuries which does not reflect the heterogeneous nature of invasively ventilated critically ill adults. Perceived contraindications to MI-E use in the acutely intubated population related to the use of increased positive pressure. There was variation in MI-E device set up and the amount of

Table 5. Reporting of adverse events (to include definitions when provided) (13/30, 43%)*

	Summary of planned adverse events data collection			Summary of adverse event reporting
1st author, year	**respiratory**	**hemodynamic**	**other**	
Clinical studies				
Sancho et al., 2003[44]				No adverse effects
Soares et al., 2014[35]				No side effects in relation to high MI-E pressures
Khan et al., 2015[42]	reintubation and pneumothorax			Reintubation 2/5 patients; pneumothorax 1/5 patient
Farina et al., 2017[33]	barotrauma, desaturation, atelectasis, haemoptysis	hemodynamic complications		None detected after MI-E
Coutinho et al., 2018[21]		HR and Mean Arterial Pressure		No significant changes
Ferreira de Camillis et al., 2018[23]	↓ oxygen saturation by 3%	occurrence of Systolic Blood Pressure <90 mmHg		None observed
Sanchez-Garcia et al., 2018[31]	barotrauma (pneumothorax) or atelectasis, desaturation, haemoptysis, other airway complications		tolerance (need for additional sedatives or analgesic medication)	No adverse events observed, well tolerated
Sanchez-Garcia et al., 2019[28]				No adverse events observed
Vokes et al., 2019[41]				Safe and feasible, no adverse effects
Guarnieri et al., 2020 (A)[43]				No adverse events observed
Martinez et al., 2021[24]	pneumothorax, SaO_2 consistently ↓ < 85% or > 10% from baseline	HR, Systolic Blood Pressure or Diastolic Blood Pressure ↑ or ↓ > 20% from baseline		10 episodes of brief desaturations or hemodynamic variations were documented during expiratory rib cage compressions + MI-E.

Table 5. *Continued*

	Summary of planned adverse events data collection			Summary of adverse event reporting
Surveys				
Prevost et al., 2010[37]				Complications (not defined) rare in Neuromuscular Disease patient, in other patient groups unknown
Rose et al., 2016[8]	mucus plugging requiring tracheostomy, pneumothorax, haemoptysis	bradycardia/asystole, hypotension, arrhythmias	chest pain	mucus plugging requiring tracheostomy (10/43, 23%) pneumothorax (4/43, 9%) haemoptysis (3/43, 7%); bradycardia/asystole (8/43, 19%) hypotension (7/42, 16%) arrhythmias (6/43, 14%) chest pain (8/43, 19%)

* Remaining articles did not explicitly report on adverse events.
Adverse events (to include definitions when provided): 13/28, 46%).*
Abbreviations: HR, heart rate; MI-E, Mechanical In- Exsufflation; SpO_2, peripheral oxygen saturation.

details reported across studies. Only three studies reported on occurrence of adverse events. Qualitative data pertaining to patient and clinician experience of using MI-E this patient group were lacking.

During invasive ventilation positive pressures breaths are delivered followed by a passive expiration. In contrast MI-E delivers both positive (insufflation) and negative (exsufflation) pressure breaths. Therefore, it is noteworthy that we found the use of positive pressure to be a perceived contraindication, whereas negative pressure was not considered a contraindication or precaution for use of MI-E in invasively ventilated critically ill adults. In these patient's lung recruitment and de-recruitment are important considerations.[45, 46] Barotrauma and volutrauma associated with large tidal volumes is well documented, and low volume lung protective ventilation is standard of care, particularly for patients with acute lung injury.[45] However, de-recruitment of lung units can have an equally adverse impact on oxygenation and effective ventilation, whilst attenuating lung injury.[46] To date, no studies have examined the extent of de-recruitment or possible adverse events in relation to a negative pressure exsufflation breath using MI-E.

Table 6. Reported barriers and facilitators to MI-E use

TDF Domain	Description
Knowledge and Skills	A perceived lack of skills ('skills') and knowledge ('knowledge') was generally seen as a barrier to use, with the suggestion that clinicians may be more skilled using the device via a trachy interface in comparison to an ETT.[8, 11]
Beliefs about consequences	Expected or potential outcomes ('beliefs about consequences') were focused on positive clinical experiences.[8, 11, 36]
Intention	A positive intent to practice ('intention').[11]
Environmental Context and resources	A lack of resources, funding and senior culture ('environmental context') impacting implementation.[8, 11, 36]
Social influences	Team culture and senior support ('social influences') influencing implementation and illustrating the potential impact colleagues.[8, 11]

TDF = Theoretical Domains Framework, ETT = endotracheal tube

Our review data indicate that MI-E is mainly studied with insufflation and exsufflation pressures of 40 cm H_2O. The use of asymmetrical pressure settings and customisation of pressure settings to endotracheal size have not yet been studied in invasively ventilated critically ill adults. Previous studies in a NMD non-ICU population[47] illustrate that asymmetrical (i.e. pressure settings to enhance the expiratory flow +30 : -40 cm H_2O) may enhance expiratory flow. One bench study examining the impact of an artificial airway on MI-E flow rates,[48] found higher pressures were required to overcome resistance to flow, particularly in narrower endotracheal tube sizes. Detail of flow rates, use of oscillations and timings were reported infrequently which makes extrapolation of device set up into a clinical setting challenging. It is difficult to know whether these omissions are simply a lack of reporting detail or whether the full potential of MI-E settings were not used; this has been commented and queried previously.[47] It should be acknowledged that advanced settings such as oscillations have not been available to clinicians for the duration of the data collection period; this may therefore have impacted on reporting of this feature. Data is needed to optimize the physiological impact of MI-E in invasively ventilated critically ill patients and to provide evidence-based guidance for our practice of care, training and education.

We found multiple outcomes reported across studies including re-intubation rates, wet sputum weight and respiratory parameters. The appropriateness of wet sputum weight as a primary outcome for examining the efficacy of MI-E is questionable.[11, 49] Although sputum clearance is important to quantify in invasively ventilated critically ill patients, a linear relationship does not exist between sputum quantity and disease severity.[3] Consistency in the selection of outcome measures across MI-E studies would allow for meta-analyses, thus strengthening the overall evidence base. Development of a core outcome measure set, as recommended by

the Comet initiative (https://www.comet-initiative.org/, accessed September 2021), that specifically focuses on airway clearance in the invasively ventilated critically ill adult population is warranted.

Only 3 studies reporting occurrence of an adverse event including pneumothoraces, haemodynamic instability and oxygen desaturation. Changes in haemodynamic parameters during MI-E were transient and did not require trial protocol cessation. Cases reports of pneumothoraces have previously been described in an adult NMD non-ICU population[50, 51] following MI-E, although no causal relationship could be confirmed due to the use of MI-E.[50-53]

A common barrier to MI-E use was a perceived lack of skills and knowledge suggesting an important opportunity for training and education. A European survey among ICU nurses showed that the knowledge related to respiration/ventilation was scored relatively low, although that would not be expected within this field of care.[54] With MI-E being part of respiratory care, further qualitative enquiry to explore barriers and facilitators in greater detail could provide useful data to inform the optimal clinical implementation of research findings.

Strength and limitations

Strengths of our scoping review are the use of systematic and transparent pre-specified protocol, a search strategy with no methodological or language restrictions, appraisal of risk of bias using the Mixed Methods Assessment Tool, and use of a theoretical framework to explore barriers and facilitators. We acknowledge that bench studies were excluded which may have provided additional data on MI-E settings in order to inform future research protocols.

CONCLUSION

This scoping review of MI-E use in invasively ventilated critically ill adults reports data on 28 studies. We conclude that there is little consistency in how MI-E is used and reported. This limits the strength of the overall body of evidence and the ability therefore to make recommendations about best practices. More studies are required, including more transparent reporting of device settings for the invasively ventilated critically ill patient. Additionally, we recommend development of a core outcome measure set for airway care clearance in this population to promote consistency in outcome reporting in future intervention trials important to patients, clinicians and researchers.

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APPENDIX 1

Methodological study assessment

The Mixed Methods Assessment Tool was completed for the 19 full-text publications. used. MMAT score for the completed randomised controlled trials (n=5) were 60%,[20] 80%[21, 22] and 100%;[23] non-randomised clinical trials (n=4) 80%[32, 36, 45] and 100%;[24, 31] and descriptive studies (n=10) 20%,[40] 60%,[38, 46] 80%[30, 34, 39, 41] and 100%.[8, 10, 11] Only 5/19 (26%) studies scored 100% (high quality).[8, 10, 11, 23, 31] Two surveys[38, 39] had relatively low response rates (16% and 37% respectively) introducing risk of selection bias. Additionally, there was a lack of detail across seven studies about potential confounders[32, 34, 36, 45] and blinding of outcome assessors.[20-22]

7 Mechanical insufflation-exsufflation for invasively ventilated critically ill patients—a focus group study

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ABSTRACT

Introduction: Mechanical Insufflation-Exsufflation (MI-E) is used as an airway clearance intervention in primary care (home ventilation), long-term care (prolonged rehabilitation after intensive care, neuromuscular diseases, and spinal cord injury), and increasingly in acute care in intensive care units (ICU).

Aim: We sought to develop in-depth understanding of factors influencing decision-making processes of healthcare professionals regarding initiation, escalation, de-escalation and discontinuation of MI-E for invasively ventilated patients including perceived barriers and facilitators to use.

Methods: We conducted focus groups (3 in the Netherlands; 1 with participants from four European countries) with clinicians representing the ICU interprofessional team and with variable experience of MI-E. The semi-structured interview guide was informed by the Theoretical Domains Framework (TDF). Two researchers independently coded data for directed content analysis using codes developed from the TDF.

Results: A purposive sample of 35 health care professionals participated. Experience varied from infrequent to several years of frequent MI-E use in different patient populations. We identified four main themes: (1) knowledge; (2) beliefs; (3) clinical decision making; and (4) future adoption.

Key findings were: (1) Participants agreed there is limited evidence with knowledge mainly derived from protocols from home ventilation centres. (2) MI-E was perceived as a safe and valuable element of airway clearance and weaning protocols in the ICU, although some safety concerns were expressed regarding required pressures. (3) MI-E was initiated and influenced by available expertise and experiences. (4) More evidence and expertise with regard to MI-E in invasively ventilated critically ill patients is needed.

Conclusion: Interprofessional knowledge and expertise of MI-E in invasively ventilated patients is limited due to minimal available evidence and adoption. Participants believed MI-E a potentially useful intervention for airway clearance and inclusion in weaning protocols when more evidence is available.

Relevance to clinical practice: This focus group study provides an overview of current practice, knowledge and expertise, and barriers and facilitators to using MI-E in mechanically ventilated patients. From these data it is evident there is a need to develop further clinical expertise and evidence of efficacy to further understand the role of MI-E as an airway clearance technique for ventilated patients.

INTRODUCTION

Patients requiring invasive ventilation often retain airway secretions, which may occlude their lower airways.[1, 2] Under normal airway conditions, cough is the dominant airway clearance mechanism.[3] In invasively ventilated patients, presence of the endotracheal tube prevents normal closing of the glottis, which is required for an effective cough. In addition, depressed level of consciousness and decreased muscle strength interfere with an adequate cough reflex.[3] Persistent presence of sputum in the airways may facilitate airway colonization, which eventually could lead to pneumonia.[4]

Removal of sputum from the airways via endotracheal suctioning is important for invasively ventilated critically ill patients.[5] However, while endotracheal suctioning can clear the trachea and upper airways of secretions, it does not reach sputum in the bronchi and smaller airways.[6, 7] Mechanical insufflation-exsufflation (MI-E) can facilitate the movement of secretions from the lower airways to the larger airways, and stimulates cough.[8, 9] It is conventionally used as a non-invasive device with rapid alternation between positive pressure to optimize tidal volume (VT) and lung recruitment followed by negative pressure that augments gas flows, improves sputum mobilization, and ultimately stimulates a cough.[10] Until now, MI-E is used extensively to promote cough and prevent secretion retention in non-critically ill patients, like patients with neuromuscular disease or spinal cord injury, that do or do not receive ventilatory support.[8]

Recent intensive care unit (ICU) practice surveys suggest increased use of MI-E as an additional intervention in airway clearance during mechanical ventilation of critically ill patients.[11-14] Of note, evidence for the effects on duration of ventilation, weaning success, and reintubation rates in invasively ventilated critically ill patients is minimal.[15] Moreover, there is little data on when to use MI-E during invasive ventilation, that is, shortly after initiation of invasive mechanical ventilation or during weaning.[15-20]

Recently, we conducted a quantitative survey of airway clearance strategies in the Netherlands.[21] We identified 16 (22%) of the 72 ICUs surveyed used MI-E as a component of airway care. Survey respondents reported use of MI-E was most commonly for patients that already use it at home, or for patients with repeated atelectasis and ongoing presence of mucus. Respondents reported different indications and contra-indications for MI-E in ICU patients and expressed uncertainty about its safety and feasibility of use during invasive ventilation.

To further understand the role of MI-E in airway clearance for critically ill invasively ventilated patients, we performed focus group interviews with ICU professionals. Our objectives were to understand perceived barriers and facilitators as well as detailed data on when and how MI-E is initiated, escalated, deescalated, and discontinued.

METHODS

Design

This is a qualitative focus group study.

Setting and participant selection

We conducted four focus groups with professionals representing the ICU interprofessional team and with variable experience of MI-E. One session was held during an international congress (EfCCNa, February 2019 Ljubljana) and three at different locations in Dutch hospitals. Locations were chosen to facilitate participants from various geographic regions in the Netherlands (Amsterdam (March), Tilburg (April) and Apeldoorn (May), 2019). All focus groups were conducted in a large private room, with a minimum of 8 and maximum of 10 participants each. Sessions did not last longer than 90 minutes. One moderator (Willemke Stilma) and one assistant moderator (Frederique Paulus or Louise Rose) were present during all sessions.

The research team were experienced in intensive care nursing (Willemke Stilma, Frederique Paulus, Louise Rose), intensive care medicine (Marcus Josephus Schultz), nursing (Lotte Verweij) and speech and language therapy (Bea Spek). One member was male (Marcus Josephus Schultz). Four researchers had experience in qualitative research (Lotte Verweij, Wilhelmina Johanna Maria Scholte op Reimer, Bea Spek, Louise Rose). The moderator and assistant moderator undertook additional training in qualitative research (Frederique Paulus and Willemke Stilma).

Using the database from our previous survey study,[21] we contacted potential participants by telephone to inform them about the study aim, required time and preparation, and date and location of the focus groups. We used purposive sampling ensuring representation from medicine, nursing and physiotherapy at every focus group. Travel costs were compensated.

Data collection

Focus groups were guided by a semi-structured interview guide developed using the Theoretical Domains Framework (TDF), a framework for cross-disciplinary implementation and behaviour change research.[22-24] The interview guide was also informed by previous work and clinical experience of the research group.[12, 14, 15, 21, 25] The interview guide (See **Table S1**) included questions about actual knowledge, skills, environmental context, (inter)professional role and beliefs regarding MI-E in invasively ventilated patients and was reviewed by health care professionals external to the research team prior to use. Each focus group had a moderator and an assistant moderator who observed, made field notes, and ensured that all participants had a chance to participate in discussion. At commencement of each session, the moderator asked participants to write down topics or questions for

discussion. Before ending each focus group, participants were asked to check if all questions and topics had been discussed. Focus groups were digitally-recorded and transcribed verbatim by a member of the research team (Willemke Stilma) with emotion detected in the audio-recording or documented in field notes added in brackets.

Data analysis

Transcripts were coded using a codebook informed by the TDF.[26] Coding comprised four phases: (1) immersive reading of transcripts; (2) initial coding based on the TDF domains; (3) identifying key concepts relating to MI-E initiation, escalation, de-escalation and discontinuation; and (4) repeated coding for final attribution.[27-29]

Coding choices and decisions were documented in a logbook. Two researchers (Willemke Stilma and Lotte Verweij) independently coded data under the supervision of more experienced researchers (Bea Spek and Louise Rose). Coding discrepancies were noted and discussed.[29] The final coding summaries grouped according to TDF domains were translated into English by an online paid translation service[30] and checked for appropriate terminology (Willemke Stilma) to enhance final discussion with the wider research team (Louise Rose, Bea Spek, Frederique Paulus).[26] TDF codes were then assembled according to four themes. Directed content analysis was used to identify key concepts within the four themes. We used MAXQDA 2020[31] for analysis. A visual presentation of the analysis is provided in the supplement **Figure S2**. Study results are reported in line with the COREQ checklist for qualitative research.[32]

Rigour and validation

The interview guide and the same moderator (Willemke Stilma) and observer (Frederique Paulus), ensured that focus groups were conducted similarly. Both had clinical experience and extensive knowledge of the evidence regarding airway clearance in the ICU. However, both had minimal direct clinical experience in MI-E for invasively ventilated patients. In addition, multiple data-analysts were involved in the coding process.[33] As a form of data validation we sent participants a session summary within a week to verify the main findings.[28, 34]

Ethical considerations

The Institutional Review Board of the Amsterdam University Medical Centres, confirmed that the Medical Research Involving Humans Subjects Acts (WMO) did not apply, waiving the need for approval (W19_028#19.047). Focus group participation was voluntary and informed consent was obtained from all individuals. All handling of personal data complies with the EU General Data Protection Regulation (GDPR).

RESULTS

Participant characteristics

We invited a purposeful sample of 42 health care professionals (doctor, nurse or physiotherapist) with experience in MI-E with ICU patients. Most participants came from the Netherlands. In the focus group held during the international conference three other European countries were represented. Seven invited professionals could not participate. In the remaining 35 participants, MI-E experience varied from recent and only in one ICU patient up to several years of frequent use in various patient populations (**Table 1**).

We identified four themes with related TDF domains and provide illustrative quotes within these domains in the supplementary material (**Table S2**). We identified four main themes: (1) knowledge; (2) beliefs; (3) clinical decision-making; and (4) future adoption.

Theme (1) Knowledge – TDF Domains: knowledge and skills

Most participants reported basing their practice on protocols and information provided by home ventilation centres. In all focus groups, participants indicated they were aware of the evidence base on MI-E with agreement that there is limited evidence for use for invasively ventilated patients. However, participants also acknowledged there is little evidence for other airway clearance interventions applied in the ICU. Participants perceived this lack of evidence to contribute to individual ICUs using their own combination of airway clearance interventions with MI-E having a modest role at times.

Due to this limited evidence base, all participants expressed a desire for more evidence on the safety, feasibility and efficacy of MI-E in invasively ventilated patients. *'When there is more knowledge, people will be more comfortable using it'* (L 114). This need included more evidence as to the most appropriate pressure and time settings and the number of sessions per day, that is, the MI-E dose.

Training provided by companies marketing MI-E was described as variable with some participants describing a good relationship that made it easy to obtain further training and information. Other participants expressed concern that there was no industry support which was challenging when a patient was transferred from an ICU already using MI-E or who used MI-E in the home.

Participants reported the main indication for MI-E was impaired cough strength. Different peak cough flow cut offs were identified (270 L/min and 160 L/min) as an indication. However, most participants described assessment of cough strength as based on subjective criteria and rarely measured objectively via a spirometer for invasively ventilated patients. Daily MI-E treatment frequency was described by participants as ranging from three to six sessions. Within a session, the number of MI-E cycles ranged from two to ten. Inspiratory pressures used on MI-E initiation

Table 1. Baseline characteristics participants focus groups (N=35)

Characteristics	**n (%)**
Participant	
ICU-Nurse	7 (20)
ICU-Nurse with additional 14 month ventilation course	9 (26)
Physician (intensivist)	3 (9)
Physiotherapist	6 (17)
Clinical Nurse Specialist	2 (6)
Type of Hospital	
Academic	13 (37)
Teaching*	12 (34)
General	2 (6)
NA**	8 (23)
Country	
The Netherlands	31 (89)
Norway	1 (3)
Denmark	2 (6)
Sweden	1 (3)
ICU beds capable of mechanical ventilation	
3-5	1 (3)
6-10	3 (9)
11-20	14 (40)
21-30	10 (29)
>30	7 (20)
Years of ICU experience	
3-5	4 (11)
6-10	10 (29)
>10	21 (60)
Years of MI-E experience	
0	1 (3)
0-2	16 (46)
3-5	7 (20)
6-10	8 (23)
>10	2 (6)

* A nonacademic hospital in which healthcare professionals are trained and educated.
**Type of hospital was not asked during the international focus group session.

ranged from 15 to 45 cmH_2O. Inspiration duration ranged from one to three seconds, with three seconds described as difficult for a patient to tolerate. Further description of reported MI-E settings is provided in **Figure 1**.

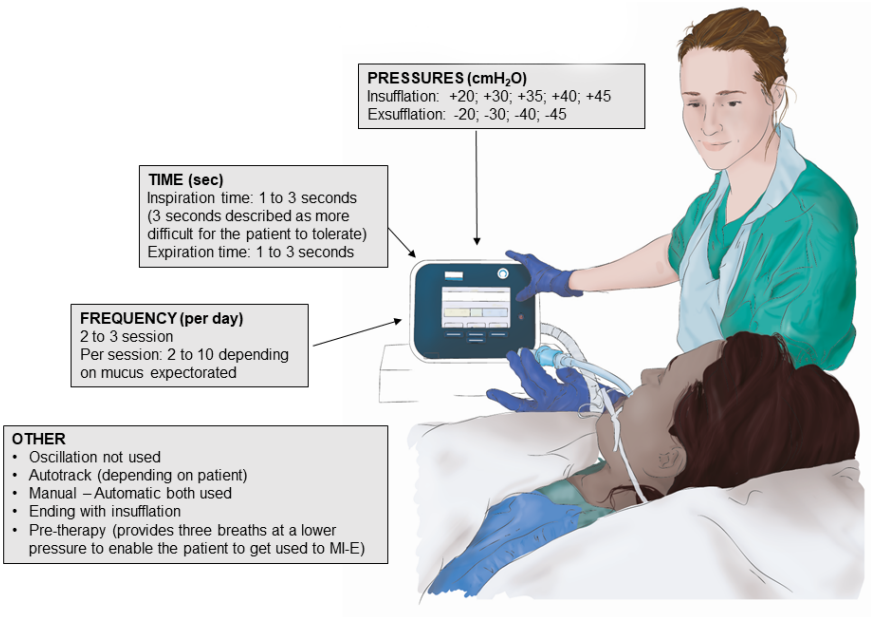

Figure 1. MI-E settings mentioned by participants
Graphical display of MI-E use in invasively ventilated patients with an overview of MI-E settings mentioned by participants. *Drawing by Marco Rosetti.*

All participants agreed a rapid switch to expiration improved mobilization of mucus and increased flow bias. However, there were practice differences around expiration duration to promote mucus mobilization. Some participants provided a pause before the next MI-E cycle, while others described rapid repetition of in- and exsufflation. Most participants completed a MI-E session with inspiration to avoid or reduce atelectasis. Few participants used oscillation with MI-E, mostly because of unfamiliarity.

Due to limited evidence, participants described uncertainty as to the effect of pressures applied during MI-E on the lungs and the resultant risk. Participants were also unsure as to the effect of MI-E on surfactant production and inflammatory response. Other uncertainties included the preferred flow settings, measuring cough strength as an indicator for use, and the need for supplemental oxygen during a MI-E session. The effect on clinical outcomes such as ventilator associated pneumonia (VAP), duration of ventilation, length of ICU stay, and weaning success were also viewed as uncertain.

Participants reported MI-E use was supported by strategies such as training

of nurses as MI-E expert users, use of protocols, and annual education. However, most reported infrequent MI-E use contributing to difficulty in developing expertise and comfort in the technique. Participants from large ICU teams reported use of pre-programmed MI-E settings as a strategy to address this lack of MI-E familiarity and to promote patient safety.

Those participants that considered themselves expert MI-E users described several tips critical to successful MI-E use. These included watching the chest rise during insufflation to ascertain sufficient pressure, listening to the chest for mucus presence, and adjusting the exsufflation pressure if still present.

Although not reported as a contraindication, in every Dutch focus group there was discussion about supplemental oxygen use with MI-E (not mentioned in the focus group conducted during the EfCCNa congress). Participants had been told either by the company supplying the MI-E device or from colleagues that using MI-E in combination with oxygen resulted in fire risk. However, participants were unsure of the accuracy of this risk.

Theme (2) Beliefs - TDF domains: goals, beliefs about consequences, and emotion

Participants identified that the main goal of MI-E was to mobilize mucus from the smaller airways. However, perceptions as to the mechanism by which this was achieved differed. Some participants saw MI-E as an imitator of natural cough; others described: *'It's a vacuum cleaner, and you're actually the glottis as well.'* (AP 634). Participants with positive experiences of MI-E believed it supports ventilator weaning and prevention of VAP. Others believed it could assist with alveolar recruitment and help to prevent atelectasis due to mucus plugging. *'First clean and then wean'* (AMS 904). Some participants thought MI-E might prevent reintubation, but remained uncertain as to this benefit. During all focus groups there was a belief that MI-E was a potential valuable element for inclusion in weaning protocols.

Most participants believed MI-E to be a potentially safer alternative to manual hyperinflation. However, participants also raised concerns about which type of invasively ventilated patients MI-E could be used safely, and how the pressure and timing settings should be adapted to prevent possible risks. Most participants believed MI-E was likely a safe adjunct during weaning, but due to lack of evidence and experience, were reluctant to use MI-E in patients with acute respiratory distress syndrome (ARDS), or after recent surgery including cardiothoracic, pulmonary or gastric by-pass. *'Of course you have the believers and the non-believers'* (AMS 852-853).

Participants expressed both positive and negative emotions associated with use of MI-E. Some described being extremely happy when they saw mucus coming out after using MI-E. This helped to generate the belief that MI-E is effective for airway clearance. Conversely, participants expressed fear of inducing a pneumothorax

by creating excess positive or negative pressure. Another fear was endotracheal or tracheostomy tube obstruction due to large amounts of mucus expectorated. *'In our case, it has been long that an intensivist would be standing next to it to be able to intubate. For either you get a plug, or there comes so much mucus that people are exhausted and become respiratory insufficient. Well then you really want someone next to you to have that….' 'a tube can be pushed in.' 'Who can act. Yes.'* (AP 1220-1223). Other participants countered this fear of adverse complications with transient desaturation identified as the most severe complication experienced using MI-E.

Theme (3) Clinical decision-making - TDF Domains: memory, attention and decision-making process, social and professional role, behavioural regulation.

Participants identified that the decision-making process to use MI-E was a collaborative one between ICU nurses, physiotherapists, and intensivists. The suggestion to trial MI-E was generally introduced by ICU nurses or physiotherapists. However, the intensivist had final responsibility for using MI-E. *'Sometimes there is a culture of how to wean the patient off a ventilator and you have a tradition of how to do it. And then, when there is a new machine, and you don't know what's the pressure and physicians don't want to, if they are not the ones who are saying we are going to use it, then it is not going to be used. So somebody has to make the decision'* (L 81-85). In other centres, nurses were so enthusiastic about MI-E that they convinced the doctors. *'The nurses have actually won the doctors over'* (T 1595).

With regard to the decision-making processes about pressures and settings used, participants identified various perspectives based on clinical reasoning. Some participants considered a physiological perspective: *'When we cough, we create a much higher pressure than we give to the patient with the MI-E. When I heard that, it did change something in my brain'* (T 688-689). Others considered MI-E pressures in the same way as applying pressure when using invasive mechanical ventilation: *'We start a little lower, but we do not dare to go above 30'* (AP 235).

In relation to the TDF domain behavioural regulation, during use of MI-E, communication and interaction with the patient was highlighted as crucial for an effective MI-E session by all participants. This patient interaction was described as taking time, in some cases up to 20 minutes, with some ICU team members not always feeling they had enough time to do this. One participant mentioned always using the 'pre-mode' that gives three breaths with lower pressures to assist a patient to get used to MI-E. Patients that were more enthusiastic about MI-E more frequently used this as it was considered easy to apply. Conversely, participants identified ICU team members frequently put little effort into motivating a patient that did not want MI-E to use it.

Another factor that influenced the decision to use MI-E was the amount of

mucus expectorated after MI-E. *'If we see a little bit or no result, I can see that we (ICU-nurses) can easily skip it'* (AMS 500). Conversely: *'And those phlegm fly into the ventilation circuit, you will be glad of it!'* (AMS 549).

The availability of other airway clearance interventions also influenced the decision to initiate MI-E. *'In regular airway care I do not miss the MI-E, because we have suctioning and with manual hyperinflation you have the same'* (AMS 387-388). For some participants, MI-E was the last resort in the various airway clearance intervention options. *'Sputum must be mobilized first... and there they have often tried bronchial toilet and everything (airway clearance techniques) and then we will use the cough machine'* (AMS 900-902).

Theme (4) Future adoption - TDF Domains: environmental context & resources, social influences.

All participants agreed that more evidence is needed to promote adoption of MI-E for critically ill invasively ventilated patients. *'We had to look at the research and if there was not good research, thus our professors says: 'No we do not do it for intensive care patients.''* (L 45-47). This evidence needs to include data on when to use MI-E in the ventilation continuum - that is, during acute respiratory failure, during weaning or after extubation to prevent reintubation, most effective MI-E settings, and evidence on the effect of MI-E on patient outcomes. All participants agreed that device availability was essential for adoption in the ICU. MI-E device availability was described as variable with some ICUs having multiple devices and others describing needing to arrange a rental device based on patient individual need such as prior use in the home.

Another factor identified as influencing adoption of MI-E for invasively ventilated patients was having ICU team members with expertise in MI-E. Physiotherapist participants described being the only team members with previous experience of MI-E in ICU. More recently in the Netherlands, physiotherapist availability in the ICU has been reduced due to organizational level changes, meaning nurses taken on the responsibility of using MI-E. However, as the experience of nurses with MI-E is highly variable, participants described decreasing use of MI-E.

Participants identified the potential benefit of using MI-E during the process of weaning for patients requiring prolonged invasive mechanical ventilation. *'It (MI-E) can also be integrated in weaning algorithms'* (L 244).

Participants reported that in long stay ICU patients, continuity and responsibility for the weaning process lies with ICU nurses. Therefore, when ICU nurses introduced MI-E they usually convinced the medical staff to attempt use. This was further made achievable for long stay ICU patients if one or two members of the ICU medical staff believed in the use of MI-E for long term weaning. Participants also reported that MI-E adoption was enhanced through a team or department decision to use it with subsequent team training.

DISCUSSION

This focus group study provides an interprofessional qualitative perspective to further understand the role of MI-E for mechanically ventilated patients in the ICU, including perceived barriers and facilitators for use. MI-E was seen as a possible adjunctive therapy to airway clearance for invasively ventilated patients, particularly as part of a long-term weaning strategy. An important barrier for use of MI-E was the lack of evidence as well as clinical experience in many centres. This barrier was reduced when expertise and positive experiences were present within the ICU team.

Most ICU professionals participating in our focus groups were familiar with the lack of evidence for MI-E in invasively ventilated patients. To contextualize this finding, our participants acknowledged that availability of evidence with regard to other frequently used airway clearance interventions is lacking but was not a barrier for their use. In addition, participants mentioned positive experiences with MI-E increased its use. In recent years, more studies on MI-E during invasive ventilation have been published.[19, 20, 25] Therefore, evidence plays an important role in the process of clinical reasoning to adopt interventions for mucus removal in invasively ventilated patients, but positive experiences are also crucial.[35] However implementation studies of interventions with a substantial evidence base such as the ABCDE bundle, demonstrate adoption is highly dependent on interprofessional collaboration and the presence of clinical champions.[36, 37]

MI-E use was not frequent in most ICUs with expertise mostly based on occasional use in patients and available protocols provided by home ventilation centres. This finding is in line with previous surveys on MI-E use in the ICU.[10, 11, 21] Participants expressed their belief in the potential for MI-E to be included in weaning protocols and routine airway clearance interventions, when evidence of efficacy is available. MI-E could provide a safe and effective intervention for mucus clearance, especially from smaller airways. Mucus clearance was seen as a large problem during the weaning process, for which ICU nurses are mainly responsible in the Netherlands.[32, 33] Participants would accept or refrain from using certain pressures and settings due to risk of harm. For example, pneumothoraxes were considered to be related to excessive positive or negative pressure. Numerous studies elucidate the effects of positive pressures during mechanical ventilation,[38-40] however little data describe the effects of applying negative pressure during invasive ventilation.

For promoting further adoption of MI-E for ventilated patients, all participants mentioned the need for more evidence within this population. Participants were looking for evidence in relation to indications for use, details on safe settings in a critically ill population and effect on outcomes like duration of ventilation. Evidence, education, and protocols need to focus specifically on indications and

settings during invasive mechanical ventilation with clear information about risks and safety. With regard to safety, all Dutch focus groups mentioned uncertainty as to the risk of fire when oxygen is added during MI-E. However, there is no reported case of such an event. Indeed, in November 2012, Philips Respironics© issued a technical statement that MI-E can be used safely in combination with oxygen for the certification of MI-E. In Dutch ICUs MI-E is delivered by using the device of Philips (Cough Assist - E 70).

Strengths and limitations

This is an interprofessional focus group study of ICU professionals representing four European countries. The study explored important issues in relation to current use and wider adoption of MI-E for invasively ventilated critically ill patients. Both the interview guide and the data analysis were based on the Theoretical Domains Framework providing a solid theoretical basis to structure our analyses and interpretation.[23]

As the focus group sessions were mainly in Dutch, a translation to English was needed to discuss findings within our international team. This translation could have altered data interpretation, although all Dutch-speaking team members speak English language fluently and are familiar with healthcare vocabulary. Second, as the selection for participating healthcare professionals was dominantly from the Netherlands, results may not reflect the situation in other countries. In addition, participants were selected based on having experience with MI-E and therefore perceived barriers from healthcare professionals with no experience at all have not been investigated. This could have resulted in an under representation of perceived barriers.

CONCLUSION

This focus group study investigated issues associated with the use of MI-E in invasively ventilated critically ill patients in Europe, predominantly the Netherlands from a multi-profession perspective. Four main themes were identified: (1) knowledge; (2) beliefs; (3) clinical decision-making; and (4) future adoption. A key finding was awareness of an insufficient evidence base and clinical expertise. Professionals perceived MI-E as a potential valuable element of airway clearance and weaning protocols in the ICU, although some safety concerns expressed regarding required pressures. A barrier to wider adoption of MI-E included the time needed to deliver the treatment. Adoption facilitators included support by the attending physician, shared decision-making, and positive experiences in terms of treatment success. Future research should focus on further developing the evidence base for MI-E as an adjunct to weaning invasively ventilated patients.

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APPENDIX

Structure for Focus group MI-E in invasively ventilated patients

Introduction (15 min):

- Moderator explains the use of the coloured cards.
- Round in which participants introduce themselves and mention their experience in MI-E.

Discussion along the following theme's (65 min):

- Education/ knowledge and skills
- Technical settings used in invasively ventilated patients
- Indications and contra-indications
- Complications
- Adjustment in work process?
- Perceptions team and colleagues?
- Competencies
- Motivation; why would you use MI-E and why not?

Closing of the session (10 min):

- Check the topics on the coloured cards.
- A summary after the transcription will be emailed. Please correct or adjust.

Table S1. Question guide for focus group MI-E in invasively ventilated patients

Domain	Key question	Prompts
Knowledge	How is MI-E used in invasively ventilated patients in your ICU?	
Skills	What specific skills are needed to use MI-E?	Are these skills present at the moment in your team? How did you train your team?
Social and professional role	Who is responsible for the decisions with regard to use of MI-E?	Physician, nurse, physiotherapist. Initiate, increase, decrease or stop treatment MI-E.
Beliefs about capabilities	How comfortable do you feel during the use of MI-E in invasively ventilated patients?	What makes you feel (un) comfortable?
Environmental context and resources	What barriers do you experience after the decision to use MI-E in invasively ventilated patients?	Are there contrary workflows or time restrictions with regard to MI-E?
Social influences	How is your decision to use MI-E influenced by the working method of your colleagues?	
Motivation	What supports your decision to initiate MI-E in invasively ventilated patients?	In what patient category would you absolutely refrain from MI-E?
Memory, attention and decision-making processes	During use of MI-E, what thoughts and clinical arguments influence the decision to adjust a MI-E treatment? What clinical argumentation do you use to refrain or stop using MI-E in invasively ventilated patients?	Required flow, flow bias, pressure in relation to patient characteristics.
Believes about the consequences	What positive effects do you perceive as a result of MI-E use in invasively ventilated patients? What negative effects do you perceive?	How does this influence the frequency of use in this population?
Goals	What is needed to promote use of MI-E in invasively ventilated patients?	Evidence, guideline, training skills, availability of device

Table S2. Illustrative quotes arranged by the TDF domains per main theme

1. Theme: Knowledge

TDF	Knowledge	Original text in Dutch
	'Of course you have the believers and the non-believers.' (AMS 852-853)	'Je hebt natuurlijk believers en de non-believers'. (AMS 852-853)
	'You experience resistance. I think on the one hand due to ignorance, unfamiliarity with the device and what it could mean for the patient.' (T 946-947)	'Je merkt dat er weerstand is. Ik denk enerzijds onwetendheid, onbekendheid met het apparaat en wat het zou kunnen betekenen voor de patiënt.' (T 946-947)
	'When there is more knowledge, people will be more comfortable using it.' (L 114)	-
	'I think in our ICU the biggest problem is that sometimes you do not know what is happening in the lungs. … And that's like, when they don't know it, they are a little … because they don't know the machine also… it's like. We do not know what is happening in those lungs, we do not want to give them big pressure. Maybe it makes more damage than it does well. I think that is one of the biggest problems.' (L 193-198)	-
TDF	**Skills**	
	'There is not structurally very much experience with the machine. Each time we have to find out a little bit, tune, with this particular patient, how we will use it.' (AP 45-47)	'Er is niet structureel erg veel ervaring met de machine. Elke keer toch weer een beetje met elkaar uitvinden, afstemmen, bij deze specifieke patiënt, hoe gaan we het doen.' (AP 45-47)
	'You can also put the suction hose on it. With a closed suction system that works ideally.' (AP 726)	'Je kunt ook de zuigslang erop zeggen. Met een gesloten zuigsysteem, dat werkt ideaal' (AP 726)
	'The technique of MI-E should be described very accurately, but that is still one thing.' (AP 360)	'Die techniek MI-E zou je heel nauwkeurig moeten beschrijven, maar dat is nog wel een ding.' (AP 360)
	'I do not think that it is lacking in education, at least I do not think that, but simply in practice, the practical part. The more you can apply it, the more familiar you become with it. Now you can easily grab that balloon, because everyone knows how to do it and the balloon is lying there too.' (AMS 423)	'Ik denk niet dat het mist aan scholing, tenminste dat vind ik niet, maar gewoon de praktijk, het praktische deel. Hoe vaker je het kan toepassen, hoe vertrouwder je ermee raakt. Nu pak je heel makkelijk die ballon, want dat kan iedereen en die licht er ook.' (AMS 423)
	'While before that time we did it manually (instead of a standard mode) and then one does it like this and the other like that. And one person feels correctly when a patient coughs and the other doesn't.' (AP 196-198)	'Terwijl voor die tijd deden we het handmatig en dan kregen we heel erg terug, ja de een doet het zo, en de ander doet het zo. En de een voelt wel aan wanneer de patiënt moet hoesten en de ander niet.' (AP 196-198)

Table S2. *Continued*

	'From in- to expiration, there is no break, but the break between it can of course make a lot of difference.' (AP 439)	'Van in naar uit, daar zit natuurlijk geen pauze, maar de pauze daartussen kan natuurlijk heel veel uitmaken.' (AP 439)
2. Theme: Beliefs		
TDF	**Beliefs about the consequences**	**Original tekst Dutch**
	'Not yet started because we do not want to expose sick lungs to the enormous pressure gradient.' (AMS 763)	'Nog niet gestart omdat we de enorme drukgradiënt op zieke longen niet los willen laten.' (AMS 763)
	'Actually I didn't even realize that it is an option to treat people with a tube with the cough machine...that flow is limited in no time, so ... Physiologically is just not logical.' (AP 103-114)	'Dat had ik me eigenlijk niet eens gerealiseerd dat het een optie is om mensen met een tube met de hoestmachine te behandelen... die flow wordt in no time gelimiteerd, dus ... Fysisch is dat eigenlijk gewoon niet logisch.' (AP 103-114)
	'They call it a cough machine, but maybe it is a sputum evacuation device'. (T 768-769)	'Ze noemen het een hoestmachine, maar misschien is het een sputum-evacuatie apparaat'. (T 768-769)
	'I am rather cautious for the upper pressure; I think that's how you make holes in the lungs.' (AMS 325-327)	'Ben eerder bang voor die bovendruk, daar maak ik die gaten mee in die longen denk ik'. (AMS 325-327)
	'We feel that we are not getting the most out of it, perhaps because we are too careful'. (AMS 235)	'We hebben het gevoel dat we er niet het maximale uithalen, misschien omdat we te voorzichtig zijn'. (AMS 235)
	'The question is what would be better? If you're going to use manual hyperinflation, in which you also give high pressures of course, but what you see is that if you connect a cough machine you might be able to mobilize the sputum slightly more controlled.' (AMS 216-219)	'De vraag is natuurlijk een beetje wat beter zou zijn. Als je gaat ballonneren, waarbij je natuurlijk ook hoge drukken geeft, maar wat je ook ziet is dat als je een hoestmachine aansluit dat je misschien iets gecontroleerder het sputum zou kunnen mobiliseren.' (AMS 216-219)
	'We had a patient with lime disease, he couldn't move at all, and we used it and it really well.' (L 179)	-
	'We had a patient in which we blew a pneumothorax with 15-15, but perhaps he would have had a pneumothorax spontaneously.' (AP 278)	'We hadden een patiënt waarbij we met 15-15 een pneu bliezen, maar misschien ook wel spontaan een pneu gehad.' (AP 278)
	'They (the patients) must allow it and do not breath against it. Then you can really use MI-E very well.' (AMS 570-572)	'Ze (de patiënten) moeten het wel toelaten en niet tegenademen. Dan kun je hem gewoon heel goed inzetten.' (AMS 570-572)
TDF	**Motivation and goals**	
	'It's a vacuum cleaner, and you're actually the glottis as well.' (AP 634)	'Het is een stofzuiger, en je bent eigenlijk ook de glottis' (AP 634)

Table S2. *Continued*

	'They must be clean first. Sputum must be mobilized first… and there they have often tried bronchial toilet and everything (airway clearance techniques) and then we will use the cough machine.' (AMS 900-902)	'Ze moeten eerst schoon. Sputum moet eerst gemobiliseerd worden… en daar hebben ze vaak bronchiaal toilet en alles geprobeerd en dan gaan wij de hoestmachine inzetten.' (AMS 900-902)
	'First clean and then wean'. (AMS 904)	'Eerst schoon en dan pas weanen'. (AMS 904)
	'Where do you work toward? Do you stop when the patient is fed up with it, or until a certain PCF? I heard a PCF 270, do you use the same numbers?' (T 642-646)	'Waar werk je naartoe? Tot de patiënt het beu is, of tot een bepaalde PCF? Ik hoorde een PCF 270, gebruiken jullie dezelfde getallen?' (T 642-646)
	'If you don't have a result with balloon and sucking, you might go on looking, but…' (AMS 430)	'Als je geen resultaat hebt met ballonneren en uitzuigen, dan ga je misschien verder kijken, maar…' (AMS 430)
	'In regular airway care I do not miss the MI-E, because we have suctioning and with manual hyperinflation you have the same.' (AMS 387-388)	'In reguliere luchtwegzorg mis ik hem niet, je kunt uitzuigen en dit aanvullen met ballonneren en dan bereik je hetzelfde.' (AMS 387-388)
	'It (MI-E) can also be integrated in weaning algoritms.' (L 244)	-
TDF	**Beliefs about capabilities**	
	'Perhaps we should do it with everyone who does not have a contraindication. So not only people with difficulty in weaning and weakness, and so on. But once you are out of the developing/increasing phase of ventilation, you could say: We'll put it (MI-E) in.' (AMS 243-246)	'Misschien moeten we het wel doen bij iedereen geen contra-indicaties heeft doen. Dus niet alleen de mensen met moeite met weanen en zwakte enzovoorts. Maar dat je zodra je uit de opbouwfase van de beademing bent, dat je dan zegt: we zetten hem erbij.' (AMS 243-246)
	'Indeed more than that, we have the impression that it (MI-E) has been very useful for those few patients we have used it'. (AP 256-259)	'Sterker nog we hebben de indruk dat het (MI-E) zeer zinvol is geweest bij die paar patiënten bij wie we het gedaan hebben'. (AP 256-259)
TDF	**Emotion**	
	'And those phlegm fly into the ventilation mask, you will be glad of it!' (AMS 549)	'En die fluimen vliegen je kapje in, daar wordt je alleen maar blij van!' (AMS 549)
	'In our case, it has been long that an intensivist would be standing next to it to be able to intubate. For either you get a plug, or there comes so much mucus that people are exhausted and become respiratory insufficient. Well then you really want someone next to you to have that….' 'a tube can be pushed in.' 'who can act. Yes.' (AP 1220-1223)	'Bij ons is het zelfs heel lang zo geweest dat er een intensivist naast stond om te kunnen intuberen. Want of je krijgt een plug, of er komt zoveel slijm dat mensen volledig uitgeput raken en insufficiënt raken. Nou dan wil je echt dat er iemand naast je hebben staan die….' 'Er een buis in kan duwen.' 'Die kan handelen. Ja.' (AP 1220-1223)

Table S2. *Continued*

3. Theme: Clinical decision-making

TDF	Memory, attention and decision processes	
	'When we cough, we create a much higher pressure than we give to the patient with the MI-E. When I heard that, it did change something in my brain'. (T 688-689)	'Als wij hoesten creëren we een veel hogere druk dan die we aan de patiënt geven met de MI-E. Toen ik dat hoorde, heeft het wel iets in mijn hersens doen veranderen'. (T 688-689)
	'We must not forget the explosive character of a cough. A normal cough goes naturally with a closed glottis initially.' (AP 604)	'En we moeten natuurlijk niet vergeten het explosieve karakter van een hoest. Een normale hoest gaat natuurlijk met een gesloten glottis aanvankelijk' (AP 604)
	'We start a little lower, but we do not dare to go above 30.' (AP 235)	'We starten wel wat lager op, maar we durven eigenlijk met goed fatsoen niet boven de 30.' (AP 235)
	'I feel that this is more positive to go at one time from a high pressure to low pressure, which does give productivity. And that you have less productivity when you use low inspiratory pressures, like 10 and exhale with 40. Then you haven't built up enough pressure in the thorax to generate that exhalation power at once.' (AP 674-677)	'Ik heb het idee dat dat positiever is en dat in een keer van een hoge druk naar een lagedruk, dat dat wel de productiviteit geeft. Dat je minder productiviteit hebt als je inspiratoir wat lage drukken, bijv met 10 en dan naar 40 gaat. Dan heb je weinig druk opgebouwd in die thorax om in een keer die kracht te genereren.' (AP 674-677)
	'Often you see the best production at the moment the pressure turns around, the patient also gets that cough stimulus. While you don't get that at the time that patient doesn't cough.' (AP 618-620)	'En vaak zie je de beste productie op het moment dat de druk zich omkeert, de patiënt ook die hoestprikkel krijgt. Terwijl je dat niet krijgt op het moment dat patiënt niet hoest.' (AP 618-620)
	'The oscillations we are still struggling with that. One patient finds it terrible and the other... I start off without and see if I have any effect. If I have no effect and the pressure cannot be higher, I will apply an oscillation to the expiration, but it is wet finger work,' (AMS 1236-1244)	'De oscillatie daar zijn we nog mee aan het stoeien. De ene patiënt vindt het verschrikkelijk en de andere... ik begin vaan zonder en kijk of ik effect heb. Als ik geen effect heb en de druk kan niet hoger, dan ga ik een oscillatie toepassen op de expiratie, maar het is natte vinger werk,' (AMS 1236-1244)
	'It seems like a simple act, but you can suddenly have a sputum problem.' (T 815-816)	'Het lijkt een simpele handeling, maar je kan wel ineens een sputumprobleem hebben.' (T 815-816)
	'Pressure drop (flow bias) is critical/essential yes.' (AP 532)	'Drukverval (flow bias) is essentieel ja' (AP 532)

Table S2. *Continued*

	'With a larger diameter, I really think you get a better delta. Where a faster one, with that cough strength, gets along. And at the moment you have a narrow tube, I think you are a lot smaller, because the time it takes until that time change is taking place because of the pressure difference, actually taking place in that lung, takes much longer. X: But it is especially of course about uh, it will be my ignorance, with regard to the bias, when you think of coughing as a physiological function, you are talking, above all, of course, about an expiratory flow. So, as far as I am concerned, this stepping up does not make much of a difference. In fact, you might say that it should be a little slower at the beginning. And that it is precisely the expiration, that should be as fast as possible. But then you will indeed be against your physical limitations.' (AP 543-555)	'Bij een grotere diameter, denk ik echt dat je een betere delta krijgt. Waarbij een snellere, waarbij je die hoestkracht meekrijgt. En op het moment dat je een smalle tube hebt, denk ik dat je een vele male kleiner is, omdat de tijd dat het duurt tot dat omslag moment door het drukverschil, ook daadwerkelijk in die long plaatsvindt, veel langer duurt. R1: maar het gaat met name natuurlijk om uh, het zal mijn onwetendheid zijn, t.a.v. de bias, als je denkt aan hoesten als een fysiologische functie, heb je het met name natuurlijk over een expiratoire flow. Dus wat mij betreft maakt die opbouw in het begin niet zoveel uit. Sterker nog, je zou kunnen zeggen dat het in het begin wat langzamer zou moeten. En dat juist de expiratie, dat die zo snel mogelijk moet. Maar dan loop je inderdaad aan tegen je fysieke beperkingen ' (AP 543-555)
	'You want to move mucus, you need something extra's. like oscillations or comprimation.' (AP 567-568)	'Wil je slijm verplaatsen, dan heb je iets extra's nodig zoals comprimeren of oscilleren.' (AP 567-568)
	'I think that at the moment you have a tube, you have a thinner diameter and a higher resistance, so the pressure you finally reach at alveolar level is lower than unintubated.' (T 699-701)	'Ik denk sowieso dat op het moment dat je een tube hebt, heb je een dunnere diameter en een hogere weerstand, dus dat de druk die je uiteindelijk op alveolair niveau bereikt, lager is dan niet geïntubeerd.' (T 699-701)
	'Yes the advantage of a tube is that there is no closing mechanism, because non-intubated patients can close their vocal cords and you can do nothing more, and that won't go if you have a tube. So that saves something again.' (AP 181)	'Ja het voordeel van een tube is dat niet zoveel tegen, want anders kunnen ze hun stembanden dichtgooien en dan kun je helemaal niks meer, en dat gaat niet als je een tube hebt. Dus dat scheelt alweer iets.' (AP 181)
TDF	**Professional role and identity**	
	'Intensivist tell us (the nurses) now that if we have to recruit or if a patient is asthmatic or difficult to ventilate, he says: Don't worry, what is 40-50? It's not a problem, up with the limits! We need ventilation. As long as there is ventilation, we accept way higher pressures now. This is a new wave.' (L 203-207)	-
	'The physiotherapist initiates MI-E, not the doctor.' (L 142)	-

Table S2. *Continued*

	'As physiotherapists we are all trained and have built up experience in using MI-E. But currently we are loosing this experience since the nurses apply the device more and more.' (AMS 609-611)	'Wij zijn als fysioteam ook helemaal geschoold en hebben als fysioteam ook ervaring opgebouwd. Dat gaan we nu geleidelijk aan verliezen omdat steeds meer vpk dat kunnen.' (AMS 609-611)
	'But in evening shifts we don't have any physiotherapists in the ICU, therefore I think that MI-E is really a task for the nurses. They can guarantee the continuity.' (AMS 620-621)	'Maar wij hebben geen avonddienst Fysio meer, en daarom is het natuurlijk ook wel echt een verpleegkundige taak. Die kunnen de continuïteit waarborgen.' (AMS 620-621)
	'If we see a little bit of no result, I can see that we (ICU-nurses) can easily skip it'. (AMS 500)	'Als we een keertje geen resultaat zien, dan denk ik dat we (IC-vpk) hem vrij makkelijk overslaan'. (AMS 500)
	'We had to look at the research and there was not good research, thus our professors says: No we do not do it for IC patients.'(L 45-47)	-
	'But if we show it, with instructions, and they (ICU-nurses) see the patient accepts it, it works, they will easily start to use it.' (T 351-352)	'Maar als we het dan voordoen, met instructie en ze (ICU-vpk) zien dat de patiënt het verdraagt dan zijn ze er eigenlijk ook heel snel mee weg.' (T 351-352)
4. Theme: Future adoption		
TDF	**Environmental context and resources**	
	'Maintenance, implement, you need to make sure you have a foundation, that there are really people who always know how to set the indication, and a button is pressed and the circus goes off. That circus must be spurred on and maintained, and yes uh... do we want it, while for the average ICU patient it is actually totally unclear what evidence is there for? Leave on patients who are in the regular wards.' (AP 1599-1604)	'Onderhoud, implementeren, je moet zorgen dat je een basis hebt, dat er echt mensen zijn die altijd weten hoe je de indicatie kunt stellen, en er wordt een knop ingedrukt en het circus gaat af. Dat circus moet wel opgetuigd zijn en ook worden onderhouden en ja uh... willen we dat wel, terwijl voor de gemiddelde IC-patiënt eigenlijk totaal onduidelijk is wat daar de evidence voor is? Laat staan bij patiënten die op de verpleegafdeling liggen.' (AP 1599-1604)
	'It occurs that somebody during the dayshift thinks about using the MI-E, and we watch the precedure and can help. But when the evening shift comes and does not feel familiar with the device, or... R7: The continuity is lacking. R4: Yes and it's hard to get comfortable in using MI-E since we hardly use it.' (AMS 368-373)	'We hebben hier nog wel eens dat de degene die dan dagdienst heeft die denkt dan, Oh ja. En dan staan we erbij en kunnen we helpen. En dan de late dienst ploeg die heeft het niet in de vingers voor hun gevoel, of uh... R7: de continuïteit is er gewoon niet. R4: Ja we krijgen het ook nooit in de vingers omdat we het zo sporadisch hier gebruiken.' (AMS 368-373)

Table S2. *Continued*

	'And with a team of 70-75 people, try to get a team of 75 men doing the same. Prospectless. R3: and that the patient has the feeling that what happens is professional and something he/she can anticipate on.' (AP 402-406)	'En bij een team van 70-75 man, probeer maar eens een team van 75 man hetzelfde te laten doen. Kansloos. R3: waarbij de patiënt het gevoel heeft dat wat gebeurt professioneel is en dat wat er gebeurt iets is waar die patiënt zich op kan instellen.' (AP 402-406)
	'So that's how we did it, we did like a drive and now everybody should learn it also the new staff' (L 100)	-
	'I do not think that it is lacking in education, at least I do not think that, but simply in practice, the practical part. The more you can apply it, the more familiar you are with it. Now you can easily grab that balloon, because that's possible for everyone and it is readily available bedside.' (AMS 422-426)	'Ik denk niet dat het mist aan scholing, tenminste dat vind ik niet, maar gewoon de praktijk, het praktische deel. Hoe vaker je het kan toepassen, hoe vertrouwder je ermee raakt. Nu pak je heel makkelijk die ballon, want dat kan iedereen en die licht er ook.' (AMS 422-426)
		'Het wordt door leken uitgevoerd. Die mensen gaan uiteindelijk naar de thuissetting, en daar is de mantelzorg, negen van de tien keer degene die de hoestmachine doet. Als ik soms zie hoe dat gaat, bij ene patiënt die wij vaak terug krijgen, die moeder sluit de patiënt, zet het apparaat aan, draait zich vervolgens om.. R1: gaat koffie zetten.. R3: en gaat een paar dingen doen, komt na 56-6 sessie terug, hangt de slang erin, zuigt twee keer en zet het ding er weer op. (gelach door aanwezigen) draait zich weer om en gaat koffie halen. Dat is natuurlijk iets wat wij ons niet kunnen voorstellen. Dat wij een patiënt alleen zouden laten, waar de hoestmachine op staat. En dat wordt dagelijks drie-vier keer gedaan. En die mensen leven nog steeds. (Veel gelach en hilariteit bij aanwezigen)... wij zien die moeder dat op de IC doen met saturaties van 60%, hangt die slang erin, terwijl we er eigenlijk al met de reanimatiekar bijna naast staan om te reanimeren. (gelach anderen) En het wordt thuis niet anders gedaan. En daarmee worden die mensen op de een of andere manier wel oud en lukt het toch. ' (AP 355-372)
	'That your organization thinks that it is required to have somebody available that will have a look at it. What cap that person has on, is irrelevant. Is that required for a successful implementation of MI-E?' (AP 1444-1447)	'Dat je organisatie vindt dat er elke dag iemand moet zijn die daarnaar kijkt. Welk petje die opheeft is niet relevant, maar iemand die verstand van zaken heeft. Is dat nodig voor een succesvolle implementatie van je hoestmachine?' (AP 1444-1447)

Table S2. *Continued*

TDF	Behavioral regulation	
	'We only have what the CTB will give with the patient. Guys please (there you go) good luck/success. Here you have a presentation, these would be good MI-E settings with him. Success. Well then you have a VP-er, we are two of us and then you start to find a way out. We have deepened ourselves and made it our own and then we have trained it with the institutions we got from the CTB. We were lucky this was a SCI patient, that could really give feedback on what he felt and what he preferred. That was our basis for the application. It even ended up in the patient taking the device to the following care institution and we trained the professionals there.' (T 1355-1366)	'Wij hebben alleen wat het CTB dan meegeeft. Jongens alsjeblieft succes. Hier hebben jullie een presentatie, dit zijn de ...M: zoek het maar uit. 'Dit zouden goede instellingen bij hem zijn. Succes. Nou dan heb je een VP-er, wij zijn met zijn tweeën en dan zoek je het maar uit. We hebbe onszelf verdiept en het onszelf eigen gemaakt en vervolgens hebben we het geschoold met de instellingen die we meekregen van het CTB. Wij hadden het voordeel dat we een patiënt met een hoge dwarsleasie hadden na een ongeval, maar dat hij zelf aanvoelde wat voor hem prettig was en wat hij wilde gebruiken. Dus op basis daarvan zijn we aan de slag gegaan. Het is zelfs zo ver gegaan dat hij het meegenomen heeft naar de zorginstelling en dat wij als VP-ers daar nog zijn geweest om het personeel te scholen. ' (T 1355-1366)
TDF	**Social influences**	
	'Yes but I think if some IC-nurses and VP-ers go to a doctor and say, you know this is just proven, sister and so...' (T 1575 onwards)	'Ja maar ik denk dat als een aantal IC-vpk en VP-ers naar en arts gaan en zeggen, weet je dit is gewoon bewezen, zus en zo...' (T 1575 en verder)
	'The nurses have actually won the doctors over'. (T 1595)	'De verpleegkundigen hebben eigenlijk de artsen over de streep getrokken'. (T 1595)
	'Sometimes there is a culture of how to wean the patient off a ventilator and you have a tradition of how to do it. And then, when there is a new machine, and you don't know what's the pressure and physicians don't want to, if they are not the ones who are saying we are going to use it, then it is not going to be used. So somebody has to make the decision.' (L81-85)	-
	'She (the patient) was very well instructable. She was self-choosing at some point, you can do it and you can't. (Chuckling others) so that work is very convenient at first. (Laughter others)' (AP 877 -879)	'Zij was heel goed instrueerbaar. Die pikte op een gegeven moment zelf uit, jij mag het wel doen en jij niet. (gegrinnik anderen) Dus dat werkt heel handig in eerste instantie. (gelach anderen)' (AP 877 -879)

Abbreviations: L=Ljubljana, AMS=Amsterdam, AP=Apeldoorn, T=Tilburg. The number behind a sentence in brackets are the line numbers in transcriptions

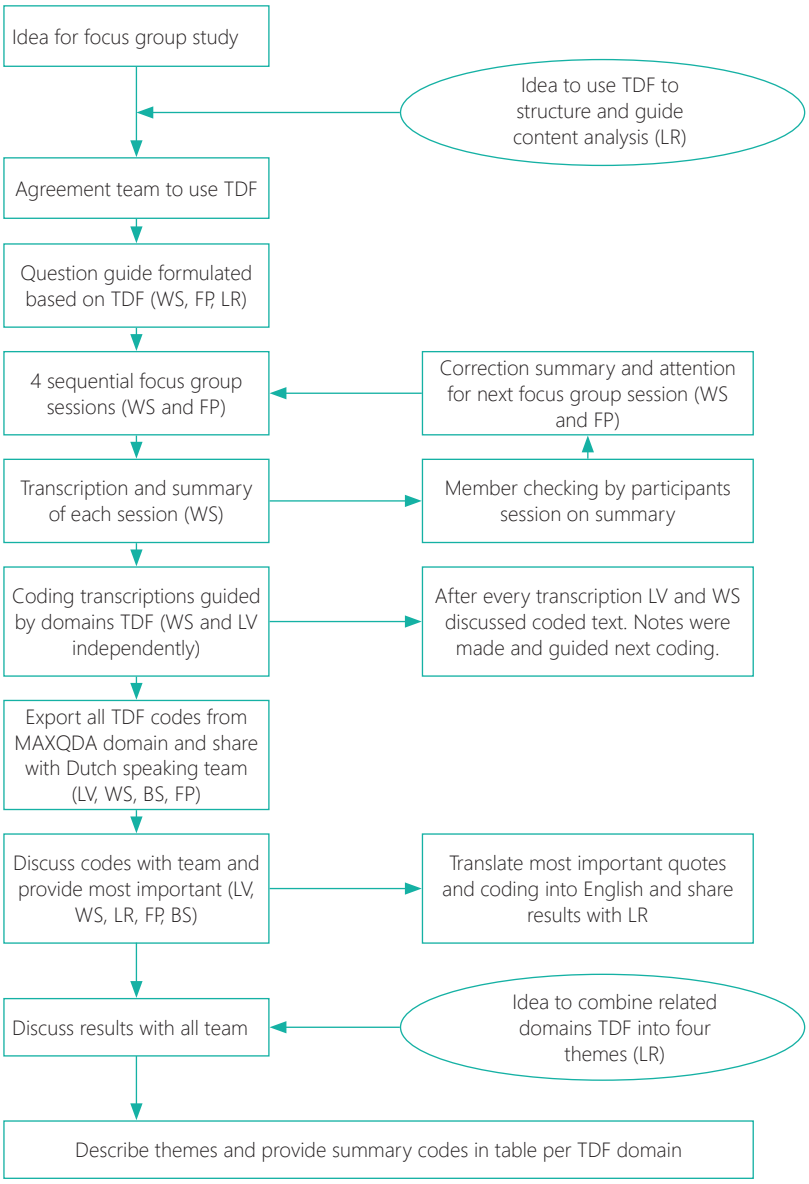

Figure S2. Focus group study data and analysis flow

Part 2

Prone positioning

8

Incidence and practice of early prone positioning in invasively ventilated COVID–19 patients—insights from the PRoVENT–COVID observational study

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ABSTRACT

We describe the incidence and practice of prone positioning and determined the association of use of prone positioning with outcomes in invasively ventilated patients with acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID–19) in a national, multicenter observational study, performed at 22 intensive care units in the Netherlands. Patients were categorized into 4 groups, based on indication for and actual use of prone positioning. The primary outcome was 28–day mortality. Secondary endpoints were 90–day mortality, and ICU and hospital length of stay. In 734 patients, prone positioning was indicated in 60%—incidence of prone positioning was higher in patients having an indication than in patients not having an indication for prone positioning (77 vs 48%, p = 0.001). Patients were left in the prone position for median 15.0 [10.5–21.0] hours per full calendar day—duration was longer in patients having an indication than in patients not having an indication for prone positioning (16.0 [11.0–23.0] vs 14.0 [10.0–19.0] hours, $p < 0.001$). Ventilator settings and ventilation parameters were not different between the 4 groups, except for FiO_2 which was higher in patients having an indication for and actually receiving prone positioning. Our data showed no difference in mortality at day 28 between the 4 groups (HR no indication, no prone vs. no indication, prone vs. indication, no prone vs. indication, prone: 1.05 (0.76–1.45) vs. 0.88 (0.62–1.26) vs. 1.15 (0.80–1.54) vs. 0.96 (0.73–1.26) (p = 0.08)). Factors associated with the use of prone positioning were ARDS severity and FiO_2. The findings of this study are that prone positioning is often used in COVID-19 patients, even in patients that have no indication for this intervention. Sessions of prone positioning lasted long. Use of prone positioning may affect outcomes.

INTRODUCTION

Patients with acute respiratory distress syndrome (ARDS) have been shown to benefit from early prone positioning if hypoxemia is severe and refractory to increases in the fraction of inspired oxygen (FiO_2) > 60% and higher positive end–expiratory pressure (PEEP).[1, 2] Especially patients with focal consolidations could profit from this intervention,[3] as higher PEEP may be ineffective and could even cause overdistension. Before the coronavirus disease 2019 (COVID–19) pandemic, prone positioning remained remarkably underused.[4, 5]

Invasively ventilated patients with ARDS due to COVID–19 often have an indication for prone positioning. Indeed, these patients often have severe hypoxemia. Additionally, consolidation may behave as focal lesions,[6, 7] which is another reason to apply prone positioning early after start of invasive ventilation,[8] Last but not least, hypoxemia could also be a consequence of pulmonary embolism, for which higher PEEP is not helpful. Several recent reports in COVID–19 patients have shown frequent use of prone positioning, but with a remarkable variance in incidence and practice.[6, 8-11]

The purpose of this current analysis of a national multicenter study of COVID–19 patients admitted to the intensive care unit (ICU) for invasive ventilation early in the pandemic, named 'PRactice of VENTilation in COVID–19' (PRoVENT–COVID),[12] was to study the incidence and practice of prone positioning in this cohort. We tested the hypothesis that prone positioning improves outcome of COVID–19 patients. We also wished to determine what factors were associated with its use.

METHODS

Study design

The PRoVENT–COVID study is an observational cohort study undertaken at 22 ICUs from the 1st of March 2020 until the 1st of June 2020 in the Netherlands—in this study, we enrolled ~40% of all patients that needed invasive ventilation during the first wave of the national outbreak.[13] The study protocol[12] and the statistical analysis plan for the current analysis were prepublished.[14]

Ethics

The study protocol was approved by the ethics committee in the Amsterdam UMC, Amsterdam, the Netherlands (registration number W20_157 # 20.171); need for individual patient informed consent was waived seen the observational nature of the study.

Study registration

The study was registered at clinicaltrials.gov at April 15, 2020 with study identifier

NCT04346342.

Inclusion and exclusion criteria

Consecutive patients were enrolled in the PRoVENT–COVID study if (1) aged > 18 years; (2) admitted to one of the participating ICUs; and (3) had received invasive ventilation for respiratory failure related to COVID–19 that was confirmed by reverse transcriptase–polymerase chain reaction for SARS–CoV–2. The PRoVENT–COVID had no exclusion criteria. For the current analysis, we excluded patients who were transferred from or to another ICU during the first days of invasive ventilation, as it could be that prone positioning was delayed because of an imminent transport and also because data on use of prone positioning could not be assessed in non–participating centers.

Collected data, and patient classification

We collected demographic data, including disease severities and the medical history at baseline. ARDS severity was scored as mild, moderate or severe, in accordance with the current definition for ARDS.[15] Ventilator settings and ventilation parameters were collected every 8 hours, and use and timing of prone positioning and use of neuromuscular blocking agents (NMBA) were collected in the first 4 calendar days of invasive ventilation. Chest X-rays and lung CT-scans were made at initiation of invasive ventilation. The X-rays were coded in quadrants and the CT-scans as a %. This was based on the interpretation of trained data collectors: all data collectors had a medical background and had received additional training regarding the chest X-rays and lung CT-scan assessment before the start of data collection. Follow–up was complete up to day 90, and included timing of liberation from invasive ventilation, ICU and hospital discharge, and life status at ICU and hospital discharge, and at day 28 and day 90.

Patients were categorized into 4 groups, based on indication for (yes or no) and the use (yes or no) of early prone positioning. A patient was labelled to have an indication for prone positioning if PaO_2/FiO_2 ratio < 150 mmHg, at PEEP of ≥ 5 cm H_2O and FiO_2 ≥ 0.6[1] for at least 2 consecutive time points within the first 32 hours after start of invasive ventilation.

Study endpoints

The primary endpoint of this analysis was 28–day mortality. Secondary outcomes were 90–day mortality, and ICU– and hospital length of stay (LOS).

Statistical analyses

We did not perform a formal sample size calculation; instead, the number of available patients served as the sample size. The day of intubation, which in theory could last from 1 minute to 23 hours and 59 minutes, was named 'day 0'. Successive

days were named 'day 1', 'day 2' and 'day 3'.

Categorical patient variables are presented as numbers and percentages, and continuous data as medians with interquartile ranges. With regard to the primary endpoint, there were no missing data. The amount of missing data of other variables was low, <5%. Incidence of prone positioning is expressed as numbers and percentages variables. Timing and duration of prone positioning are expressed in the number of hours from start of invasive ventilation, and total number of hours per full calendar day. To assess differences among the 4 groups a chi–squared test and Kruskal–Wallis test were used where appropriate.

Ventilatory variables and parameters over the first 4 calendar days were compared using a Kruskal–Wallis test and were presented in cumulative distribution plots and line graphs displaying the 4 groups of interest. For each day, ventilatory variables at the moment of the worst PaO_2/FiO_2 for that day were used, assuming these were collected at the moment the patient was in a supine position.

Hazard ratios (HRs) for 28–day and 90–day mortality was compared between the 4 groups using a (shared–frailty) Cox proportional hazard model, with center as frailty. HRs for ICU length of stay and hospital length of stay were compared using a competing risk analysis with center as random effect. Kaplan–Meier curves were constructed for all outcomes of interest. Predefined variables assessed for the final models were severity of ARDS,[10] PEEP, FiO_2, body mass index (BMI), use of NMBAs and tidal volume per predicted body weight. If these variables had a $p < 0.20$ in the univariable model, they were included in the multivariable model. Covariates used for the final model were the variables with a $p < 0.05$ in the multivariable model; the covariates used in the univariable, and multivariable models are reported in **Supplementary Table S1**. This analysis was repeated to compare patients having an indication for and receiving prone positioning and patients having an indication for but not receiving prone positioning.

An adjusted mixed–effect model with center as random effect was used to determine which factors had an association with use of prone positioning. Variables included in this model were severity of ARDS,[16] PEEP, FiO_2, body mass index (BMI) and hypercapnia.

As a posthoc analysis, a time-dependent Cox regression analysis was performed. All models were checked for collinearity. All models were checked for collinearity. All analyses were conducted in R v.4.0.3 (R Foundation for Statistical Computing: Vienna, Austria)[17] and a $P < 0.05$ was considered significant.

RESULTS

Patients enrolled

Between March 1 and June 1, 2020, 22 ICUs were invited and accepted participation in the PRoVENT-COVID study. Of 1122 enrolled patients, 734 patients were eligible

for the current analysis. The main reason for exclusion was an early transfer from or to a nonparticipating hospital (**Figure 1**). At the start of ventilation, patients that were placed in prone positioning had higher severities of ARDS, and PaO_2/FiO_2 < 150 was more frequent in patients that had an indication for prone positioning (**Table 1**). Additionally, in the group without an indication for prone positioning, the severity of ARDS and the number of patients with a PaO_2/FiO_2 ≤ 150 mm Hg was higher in the group that received prone positioning than the group that was not placed in the prone position (**Table 1**). NMBAs were used more often in patients having an indication than in patients not having an indication for prone positioning (60 vs. 52%).

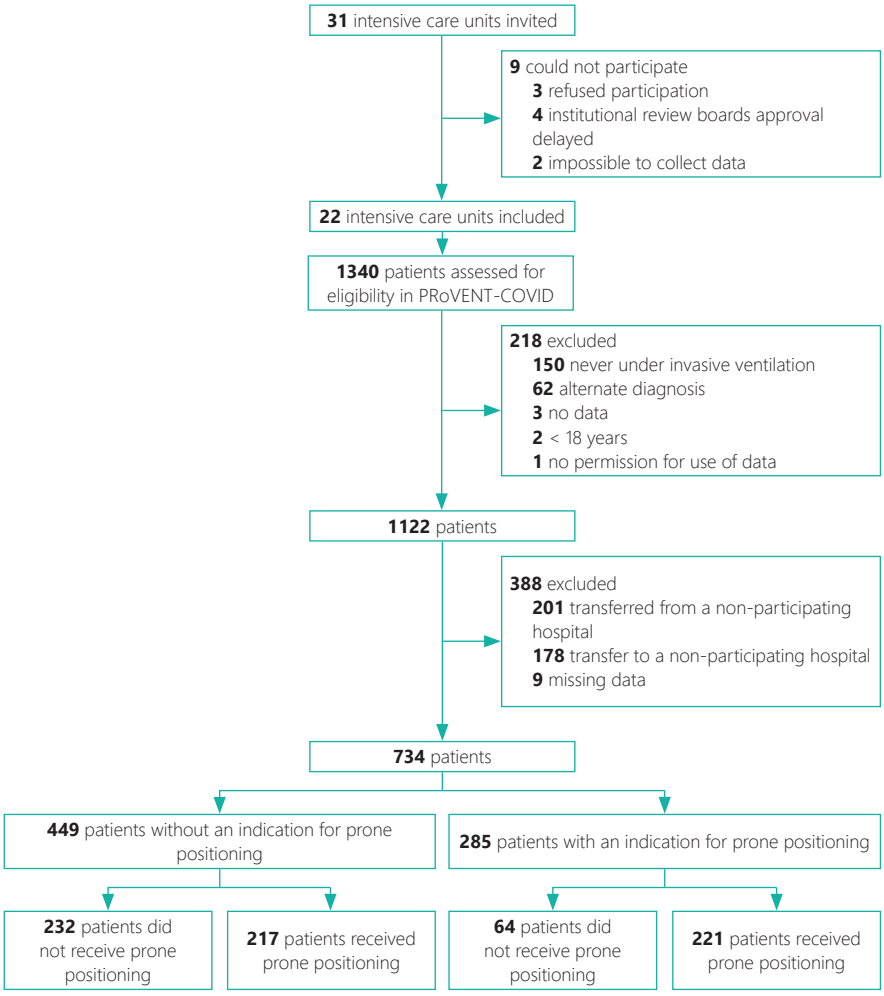

Figure 1. Flow chart of patient inclusion

Table 1. Baseline characteristics

	without an indication for prone positioning			with an indication for prone positioning		
	no prone positioning (N = 232)	**prone positioning (N = 217)**	***P* value**	**no prone positioning (N = 64)**	**prone positioning (N = 221)**	***P* value**
Age, years (median, IQR)	64.2 (11.4)	65.0 (10.3)	0.430	66.6 (9.1)	62.6 (11.2)	0.008
Male gender, N (%)	171 (73.7)	164 (73.2)	0.916	46 (71.9)	154 (69.1)	0.758
BMI, kg/m^2 (median, IQR)	28.5 (7.8)	28.1 (4.0)	0.490	29.2 (6.3)	29.3 (5.3)	0.841
Chest CT performed, N (%)	93 (40.1)	82 (36.6)	0.500	17 (26.6)	92 (41.3)	0.040
Affected lung parenchyma (%)	5 (5.3)	2 (2.4)	0.212	0 (0.0)	2 (2.2)	0.967
≤ 25%	28 (29.8)	28 (34.1)		6 (35.3)	27 (29.0)	
50%	34 (36.2)	19 (23.2)		5 (29.4)	30 (32.3)	
75%	21 (22.3)	28 (34.1)		5 (29.4)	29 (31.2)	
100%	6 (6.4)	5 (6.1)		1 (5.9)	5 (5.4)	
Chest X-ray performed, N (%)	127 (91.4)	135 (93.8)	0.501	44 (93.6)	113 (85.6)	0.199
Number of quadrants affected (%)			0.760			0.790
1	10 (7.9)	10 (7.4)		2 (4.5)	8 (7.0)	
2	27 (21.4)	36 (26.7)		9 (20.5)	27 (23.7)	
3	31 (24.6)	34 (25.2)		16 (36.4)	32 (28.1)	
4	58 (46.0)	55 (40.7)		17 (38.6)	47 (41.2)	
Pneumothorax, N (%)	0 (0.0)	0 (0.0)	1.000	0 (0.0)	1 (16.7)	1.000
Severity of illness						
SAPS II (median, IQR)	35.7 (11.7)	36.9 (12.8)	0.562	35.9 (16.1)	37.1 (12.8)	0.726
APACHE II (median, IQR)	16.6 (11.3)	18.9 (8.5)	0.230	16.1 (8.0)	19.6 (9.3)	0.295

Table 1. *Continued*

	without an indication for prone positioning			with an indication for prone positioning		
	no prone positioning (N = 232)	**prone positioning (N = 217)**	***P* value**	**no prone positioning (N = 64)**	**prone positioning (N = 221)**	***P* value**
APACHE IV (median, IQR)	55.2 (20.5)	59.6 (22.9)	0.197	67.2 (25.0)	58.6 (20.6)	0.086
SOFA (median, IQR)	8.1 (3.2)	9.1 (4.4)	0.066	8.6 (3.2)	8.1 (3.8)	0.512
Severity class ARDS (%)			0.002			0.607
Mild	82 (36.3)	51 (23.5)		0 (0.0)	2 (0.9)	
Moderate	142 (62.8)	157 (72.4)		49 (76.6)	154 (69.4)	
Severe	2 (0.9)	9 (4.1)		15 (23.4)	66 (29.7)	
$PaO_2/FiO_2 \leq 150$ mm Hg, N (%)	90 (38.8)	104 (47.9)	0.024	56 (87.5)	189 (85.5)	0.600
Medical history						
None	57 (24.6)	46 (20.5)	0.315	14 (21.9)	60 (26.9)	0.517
Hypertension, N (%)	75 (32.3)	75 (33.5)	0.842	26 (40.6)	73 (32.7)	0.296
Heart failure, N (%)	13 (5.6)	12 (5.4)	1.000	4 (6.2)	7 (3.1)	0.271
Diabetes, N (%)	43 (18.5)	57 (25.4)	0.089	12 (18.8)	52 (23.3)	0.499
Chronic kidney disease (%)	9 (3.9)	9 (4.0)	1.000	2 (3.1)	7 (3.1)	1.000
Baseline creatinine, µmol/L (median, IQR)	81.1 (37.2)	96.2 (79.7)	0.021	93.2 (48.1)	82.5 (39.8)	0.121
Liver cirrhosis, N (%)	1 (0.4)	0 (0.0)	1.000	1 (1.6)	0 (0.0)	0.223
COPD, N (%)	16 (6.9)	17 (7.6)	0.857	5 (7.8)	24 (10.8)	0.640
Active hematological neoplasia, N (%)	5 (2.2)	4 (1.8)	1.000	2 (3.1)	0 (0.0)	0.049
Active solid neoplasia, N (%)	6 (2.6)	9 (4.0)	0.440	0 (0.0)	5 (2.2)	0.590
Neuromuscular disease, N (%)	1 (0.4)	0 (0.0)	1.000	0 (0.0)	5 (2.2)	0.590

Immunosuppression, N (%)	10 (4.3)	5 (2.2)	0.295	1 (1.6)	5 (2.2)	1.000
Home medication						
Systemic steroids, N (%)	13 (5.6)	9 (4.0)	0.515	3 (4.7)	5 (2.2)	0.383
Inhalation steroids, N (%)	26 (11.2)	24 (10.7)	0.882	7 (10.9)	29 (13.0)	0.831
ACE inhibitor, N (%)	44 (19.0)	48 (21.4)	0.560	7 (10.9)	38 (17.0)	0.329
Angiotensin II receptor blocker, N (%)	22 (9.5)	29 (12.9)	0.298	9 (14.1)	21 (9.4)	0.352
Beta blocker, N (%)	44 (19.0)	43 (19.2)	1.000	18 (28.1)	43 (19.3)	0.165
Insulin, N (%)	17 (7.3)	21 (9.4)	0.499	1 (1.6)	9 (4.0)	0.467
Metformin, N (%)	32 (13.8)	44 (19.6)	0.103	7 (10.9)	36 (16.1)	0.426
Statin, N (%)	63 (27.2)	76 (33.9)	0.127	18 (28.1)	76 (34.1)	0.450
Calcium channel blockers, N (%)	31 (13.4)	49 (21.9)	0.019	15 (23.4)	39 (17.5)	0.281

Abbreviations: ACE inhibitor, Angiotensin-converting enzyme inhibitor; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, Acute respiratory distress syndrome; COPD, Chronic obstructive pulmonary disease; IQR, interquartile range; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; BMI, body mass index.

Incidence of prone positioning

Prone positioning was used in 438/734 (60%) patients. Incidence of prone positioning was higher in patients having an indication than in patients not having an indication for prone positioning (77 vs 48%; $p < 0.001$). For patients who were placed in the prone position, the median first day of proning was day 0 [0 to 1] and received prone positioning over a median of 3 [2 to 3] days; this was similar in patients with and without an indication. Prone positioning lasted median 16.0 [11.0 to 23.0] hours per full calendar day in patients having an indication, and 14.0 [10.0 to 19.0] hours in patients without an indication ($p < 0.001$) (**Table 2** and **Figure 2**).

Table 2. Duration of Prone Positioning

	no indication for prone positioning (N = 217)	**indication for prone positioning (N = 221)**	***P* value**
Day 0			
n/N (%)	110/217 (51)	130/221 (59)	
absolute time in a prone position, hours (median, IQR)	7.5 [3.6 to 12.0]	10.0 [6.0 to 14.4]	0.008
relative time in a prone position, % of total hours*	75% [65 to 75]	100% [80 to 100]	<0.001
Day 1			
n/N (%)	167/217 (77)	180/221 (81)	
absolute time in a prone position, hours (median, IQR)	15 [10.0 to 20.5]	16 [11.9 to 23.1]	0.016
relative time in a prone position, % of total hours	63% [42 to 85]	67% [50 to 96]	0.016
Day 2			
N (%)	147/217 (68)	175/221 (79)	
absolute time in a prone position, hours (median, IQR)	12.5 [9.0 to 18.8]	16 [10.5 to 23.5]	< 0.001
relative time in a prone position, % of total hours*	52% [38 to 78]	67% [44 to 98]	< 0.001
Day 3			
n/N (%)	143/217 (66)	152/221 (66)	
absolute time in a prone position, hours (median, IQR)	13.8 [10.3 to 18.0]	16.0 [11.0 to 22.0]	0.039
relative time in a prone position, % of total hours*	58% [43 to 75]	67% [46 to 92]	0.039
Total			
Duration of prone positioning per full calendar day (median, IQR)	14.0 [10.0 to 19.0]	16.0 [11.0 to 23.0]	< 0.001

*Calendar day 0 could last from 0 to 24 hours; in patients with no indication day 0 had 10.0 [5.5 – 16.1] hours, in patients with an indication day 0 had 10.3 [6.0 – 18.1] hours.

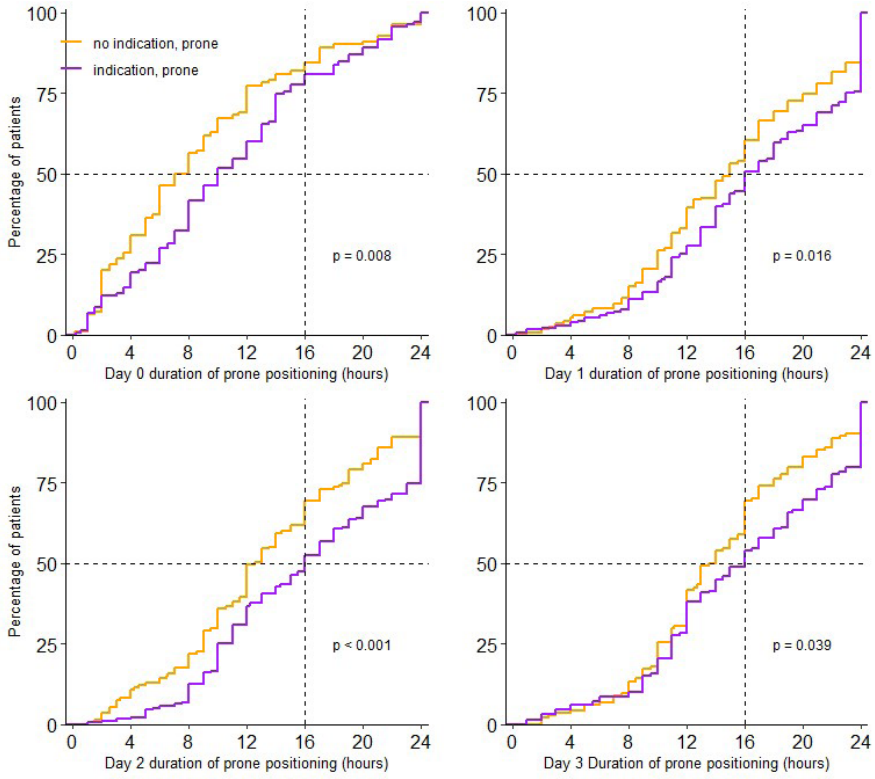

Figure 2. Cumulative distribution duration of prone positioning per day
Duration of prone positioning session for each patient on day 0 to day 3.

Ventilation characteristics in the first 4 calendar days of ventilation

At start of ventilation, peak airway pressure, driving pressure, compliance, respiratory rate, FiO_2, PaO_2, and SaO_2/FiO_2 and PaO_2/FiO_2, and mechanical power was different between the 4 groups (**Table 3**). In the group without an indication for prone positioning, invasive ventilation differed with regard to the peak and driving pressure. Both were higher in the patients that received prone positioning (**Table 3**). Driving pressure, compliance, PaO_2/FiO_2, FiO_2 and $PaCO_2$ remained different between groups on successive days. Tidal volume was not different between groups, on any day of collection of these data. PEEP was only different at day 2 and day 3; PaO_2 was different at day 0 and day 1 (**Figure 3** and **4**, **Supplementary Figures S1** to **S8**).

Table 3. Ventilatory Characteristics at Start of Ventilation.

	without an indication for prone positioning			with an indication for prone positioning		
	no prone positioning (N = 232)	**prone positioning (N = 217)**	***P* value**	**no prone positioning (N = 64)**	**prone positioning (N = 221)**	***P* value**
Mode of ventilation	232	217		64	221	
Volume Control	23 (10.0)	51 (22.8)		6 (9.4)	32 (14.5)	
Pressure Control	127 (55.5)	116 (51.8)		33 (51.6)	131 (59.3)	
Pressure Support	7 (3.1)	4 (1.8)		0 (0.0)	8 (3.6)	
SIMV	17 (7.4)	24 (10.7)		11 (17.2)	19 (8.6)	
APRV	6 (2.6)	7 (3.1)		0 (0.0)	9 (4.1)	
Intellivent-ASV	11 (4.8)	6 (2.7)		3 (4.7)	5 (2.3)	
other	38 (16.6)	16 (7.1)		11 (17.2)	17 (7.7)	
Vt, mL/kg PBW (median, IQR)	6.2 [5.7 - 6.9]	6.2 [5.7, 6.8]	0.561	6.3 [5.9 - 7.1]	6.2 [5.7 - 7.0]	0.295
PEEP (median, IQR)	12.0 [10.0 - 15.0]	12.0 [10.0 - 15.0]	0.419	12.0 [10.0 - 14.0]	12.0 [10.0 - 14.8]	0.848
Ppeak (median, IQR)	25.5 [23.0 - 29.0]	27.0 [24.0 - 30.0]	0.022	27.0 [24.0 - 30.0]	28.0 [25.0 - 32.0]	0.106
Driving pressure (median, IQR)	13.3 [12.0 - 16.0]	15.0 [12.0 - 16.8]	0.059	14.0 [13.0 - 16.2]	15.7 [13.0 - 18.2]	0.030
Mechanical power (median, IQR)	17.0 [13.2 - 19.8]	16.4 [13.6 - 19.8]	0.861	17.7 [13.9 - 21.4]	18.1 [14.8 - 22.6]	0.418
Compliance (median, IQR)	31.8 [26.1 - 40.6]	29.5 [24.1 - 38.2]	0.120	32.3 [26.0 - 38.2]	28.7 [22.3 - 34.5]	0.039
Total respiratory rate (median, IQR)	20.0 [18.0 - 22.8]	20.0 [20.0 - 24.0]	0.136	20.0 [18.0 - 21.5]	21.0 [18.0 - 25.0]	0.014
FiO_2 (median, IQR)	0.6 [0.5 - 0.8]	0.6 [0.5 - 0.8]	0.127	0.7 [0.6 - 0.8]	0.8 [0.7 - 1.0]	0.016
SpO_2/FiO_2 ratio (median, IQR)	158.3 [125.5 - 192.1]	153.3 [116.7 - 180.0]	0.022	129.0 [109.1 - 141.5]	115.1 [96.2 - 136.5]	0.012
End tidal CO2 mmHg (median, IQR)	4.8 [4.3 - 5.5]	4.8 [4.2 - 5.5]	0.889	4.7 [4.3 - 5.6]	4.9 [4.3 - 5.7]	0.291
NMBA	89 (38.4)	116 (51.8)	0.005	27 (42.2)	133 (59.6)	0.015

Vital signs						
Mean arterial pressure, mmHg (median, IQR)	82.5 [72.0 - 98.0]	86.0 [75.0 - 101.0]	0.106	87.0 [74.0 - 7.2]	88.5 [75.0 - 05.2]	0.386
Heart rate, beats per min (median, IQR)	89.0 [77.0 - 105.5]	91.0 [78.0 - 105.0]	0.380	88.5 [76.5 - 00.2]	96.0 [83.0 - 112.0]	0.002
Laboratory tests						
pH (median, IQR)	7.4 [7.3 - 7.4]	7.4 [7.3 - 7.4]	0.083	7.4 [7.3 - 7.4]	7.3 [7.3 - 7.4]	0.224
PaO_2 (median, IQR)	12.3 [10.1 - 15.6]	11.2 [9.5 - 13.8]	0.001	10.4 [9.3 - 11.8]	10.1 [8.9 - 11.4]	0.173
PaO_2/FiO_2 ratio (median, IQR)	161.5 [118.8 - 212.9]	143.8 [106.5 - 181.3]	0.005	108.8 [92.2 - 132.0]	96.4 [79.2 - 119.2]	0.005
$PaCO_2$ (median, IQR)	5.5 [4.7 - 6.1]	5.6 [4.9 - 6.5]	0.037	5.9 [5.0 - 6.7]	6.2 [5.3 - 7.3]	0.031
Lactate (median, IQR)	1.2 [0.9 - 1.5]	1.2 [0.9 - 1.5]	0.713	1.2 [1.0 - 1.6]	1.2 [0.9 - 1.5]	0.466
Creatinine, µmol/L (median, IQR)	72.0 [58.0 - 91.0]	74.0 [62.0 - 100.0]	0.111	80.0 [68.0 - 96.0]	74.0 [57.0 - 91.2]	0.086

Abbreviations: SIMV: Synchronized intermittent mandatory ventilation, ASV: Adaptive Support Ventilation, APRV: Airway pressure release ventilation, PBW: predicted bodyweight, NMBA: neuromuscular blocking agents, Vt, Tidal Volume.

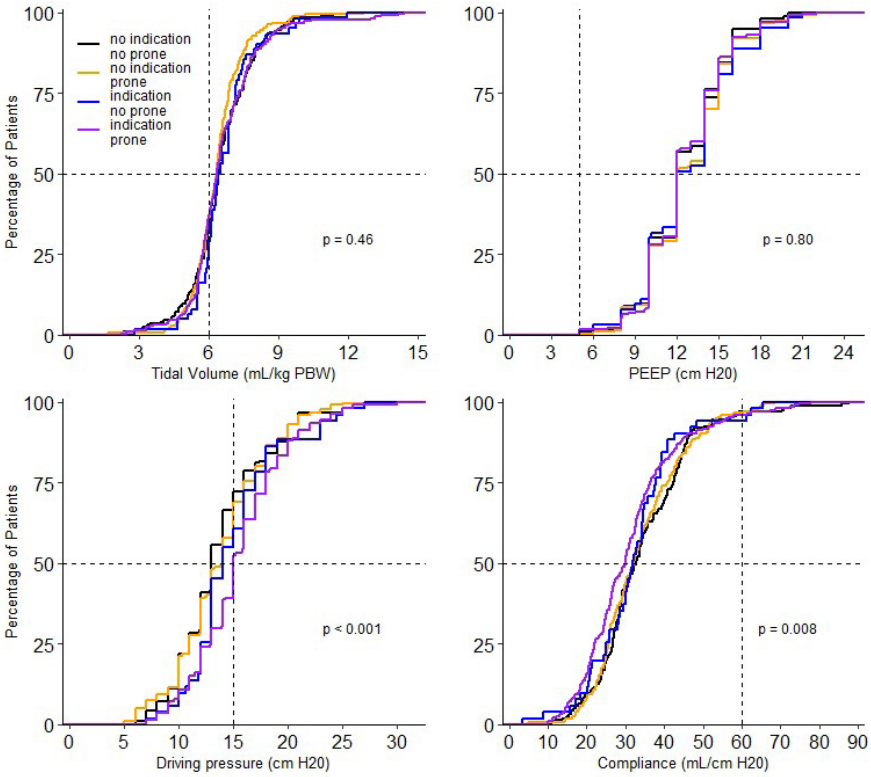

Figure 3. Cumulative distribution of ventilatory parameters on day 0
Levels of tidal volume, PEEP, driving pressure and compliance for each patient on day 0.

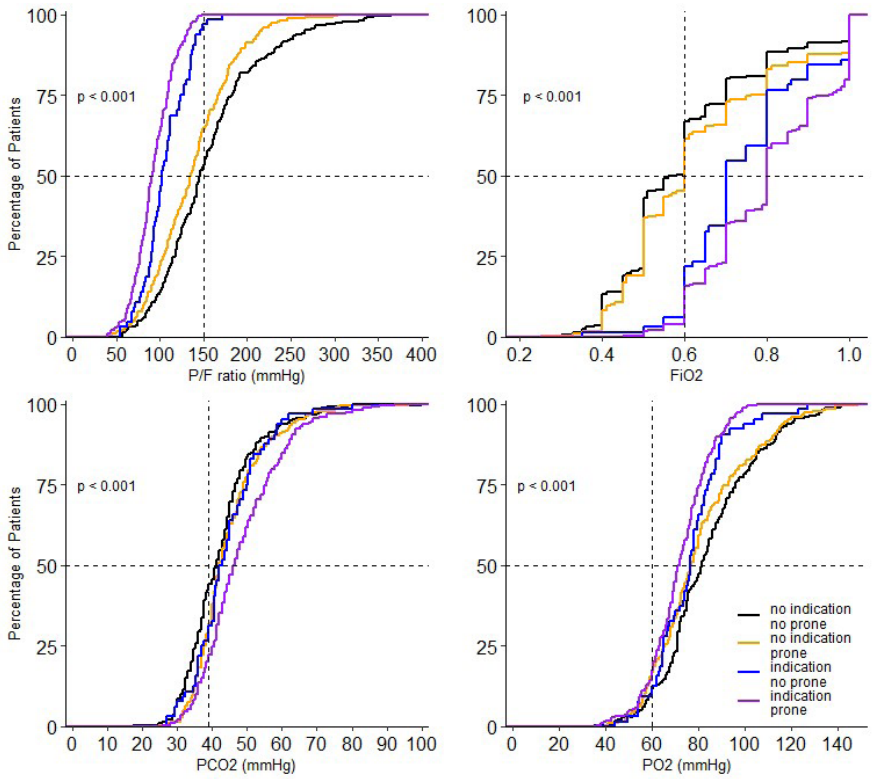

Figure 4. Cumulative distribution of parameters of gas exchange on day 0
Levels of P/F ratio, FiO_2, PO_2 and PCO_2 for each patient on day 0.

Patient outcomes

Mortality at day 28 was lowest in patients with no indication for prone positioning—28.6% vs 31.3% in patients that were not placed in prone position vs patients that were placed in prone position. Mortality at day 28 was highest in patients with an indication for prone positioning—41.3% vs 34.1% in patients that were not placed in prone position vs patients that were placed in prone position. Differences between the 4 groups, though, did not reach statistical significance (p 0.244). Differences in mortality at day 90 between groups followed a similar pattern (p 0.100).

ICU length of stay in patients that survived till ICU discharge was lower in patients that had no indication for prone positioning—median 16 [10 to 25] days vs 19 [12 to 33] days, in patients that were not placed in prone position vs patients that were placed in prone position. ICU length of stay in patients that survived till ICU discharge was higher in patients that had an indication for prone positioning—median 22 [12 to 30] days vs 21 [14 to 34] days in patients that were not placed in prone position vs patients that were placed in prone position.

Hospital length of stay in patients that survived till hospital discharge was lower in patients with no indication for prone positioning—median 28 [20 to 40] days vs 31 [22 to 51] days in patients that were not placed in prone position vs patients that were placed in prone position. Hospital length of stay in patients that survived till hospital discharge was higher in patients with an indication for prone positioning—median 31 [21 to 44] days vs 35 [24 to 50] days in patients that were not placed in prone position vs patients that were placed in prone position.

Ventilator free days at day 28 were higher in patients with no indication for prone positioning—a median of 7.0 (0.0–17.5) days vs. 1.0 (0.0–17.00) days, in patients that were not placed in the prone position vs. patients that were placed in the prone position. Ventilator free days at day 28 were low in patients with an indication for prone positioning— a median of 0.0 (0.0–10.0) days vs. 0.0 (0.0–14.0) days, in patients that were not placed in a prone position vs. patients that were placed in a prone position.

Adjusted HRs were different between groups for mortality at day 90, ICU length of stay and hospital length of stay, but not for mortality at day 28 (**Figure 5** and **Supplementary Figure S9**).

Factors that have an association with use of prone positioning

ARDS severity and FiO_2 were the only factors that were independently associated with the actual use of prone positioning (**Supplementary Table S2**).

Post Hoc Analysis

The time-dependent Cox regression analysis did not change the findings (**Supplementary Table S3**).

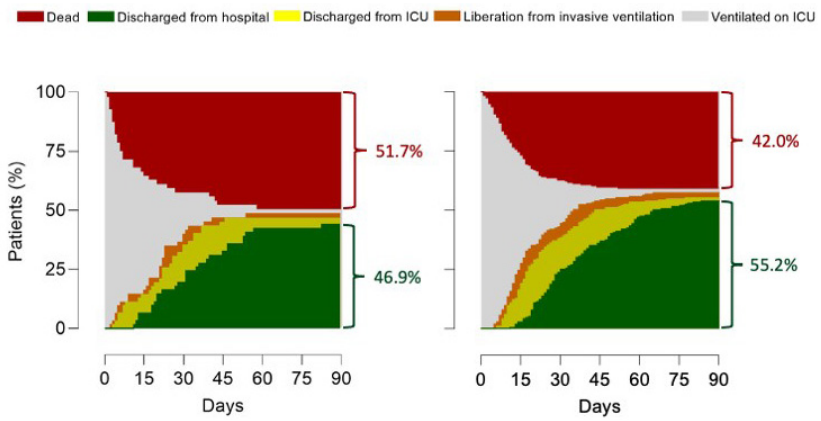

Figure 5. Outcomes
Patient outcomes for the groups of patients with an indication for prone positioning, on the left panel patients are displayed that did not receive prone positioning; on the right panel patients are displayed that did receive prone positioning.

HR's for outcomes were (no indication, no prone vs. no indication, prone vs. indication, no prone vs. indication, prone)
28-day mortality: 1.05 [0.76 – 1.45] vs. 0.88 [0.62 – 1.26] vs. 1.15 [0.80 – 1.54] vs. 0.96 [0.73 – 1.26] (P = 0.08)
90-day mortality: 0.93 [0.67 - 1.27] vs. 0.89 [0.64 - 1.24] vs. 1.19 [0.88 - 1.62] vs. 0.99 [0.76 - 1.28] (P = 0.02)
ICU discharge: 1.28 [1.02 – 1.61] vs. 1.03 [0.80 – 1.33] vs. 0.88 [0.69 – 1.12] vs. 0.89 [0.74 – 1.08] (P = 0.02)
Hospital discharge: 1.25 [0.99 – 1.58] vs. 1.07 [0.83 – 1.39] vs. 0.88 [0.69 – 1.13] vs. [0.89 [0.73 – 1.08] (P = 0.01)
HR's for outcomes in the groups with an indication were (indication, no prone vs. indication, prone)
28-day mortality: 1.30 [0.82 – 2.07 vs. 0.76 [0.48 – 1.21] (P = 0.25)
90-day mortality: 1.41 [0.93 - 2.14] vs. 0.70 [0.46 - 1.07] (P = 0.10)
ICU discharge: 0.77 [0.52 - 1.14] vs. 1.29 [0.87 – 1.91] (P = 0.93)
Hospital discharge: 0.78 [0.52 – 1.18] vs. 1.26 [0.84 – 1.90] (P = 0.70)

DISCUSSION

Here, we describe the practice and outcome of prone positioning in patients with ARDS due to COVID-19 that received invasive ventilation in the first 3 months of the national outbreak in the Netherlands. The incidence of prone positioning was high, also in patients not having an indication for this intervention. Sessions of prone positioning were long and lasted longer in patients with an indication. ARDS severity and FiO_2 predicted the use of prone positioning.

Our study confirms the high incidence of prone positioning in invasively ventilated COVID-19 patients, as found in other observational studies.[6,9,11,18] Studies from before the COVID-19 pandemic showed a remarkable underuse of this intervention in patients with ARDS—in the LUNG SAFE study in 2014, overall use was 7.9%, and 16.3% in patients with severe ARDS;[19] in the APRONET study in

2016, overall use was 13.7%, and 32.9% of patients with severe ARDS.[5] There are several reasons why prone positioning is used more often in COVID-19 patients. It could simply be that the increase of use has continued after LUNG SAFE and APRONET—the implementation of interventions with proven benefits can take many years, also in the ICU setting.[20] It could also be that the poor results of randomized clinical trials that tested alternative ways to improve outcomes, like higher PEEP and recruitment maneuvers, have had a positive effect on the use of prone positioning. Last but not least, it could be that COVID-19 ARDS presents as a form of lung injury that may respond better to prone positioning than other forms of ARDS.[3] Indeed, the findings of one randomized clinical trial suggest that prone positioning may be better than higher PEEP in ARDS patients with non-recruitable lung lesions, which may be typical in COVID-19 ARDS, at least at the initiation of invasive ventilation.[3,21]

The high incidence of prone positioning was notable in patients not having an indication for this intervention. This may also have been the case in other cohorts, as the reported overall PaO_2/FiO_2 ratio in other studies were comparable to that in our cohort,[5, 8, 14] suggesting a similar distribution of ARDS severities and with that a comparable rate of indication for prone positioning. In addition, some of the patients without an indication for prone positioning were actually placed in the prone position. This group had median lower PaO_2/FiO_2 ratios, which could be seen as an indication to initiate prone positioning by the clinician. Whether the results of the chest X-rays and lung CT-scans were an indication for the clinician to initiate prone positioning could not be collected. Therefore, we could not comment on or analyze the relationship between imaging and the indication for prone positioning in this cohort.

In our data, there was no difference in mortality at day 28 between groups, but there was a difference in mortality at day 90. Duration of invasive ventilation is remarkably high in COVID-19 patients, and so is LOS in ICU in these patients.[23] This can explain why 28-day mortality was not different between the groups, while 90-day mortality was. On the one hand, it could suggest the benefit of this intervention in ARDS due to COVID-19, in line with the findings of the seminal study in patients with ARDS not related to COVID-19 in France.[1] This finding is also in line with the results of one metaanalysis of studies in invasively ventilated COVID-19 patients.[23] On the other hand, it could be that this intervention was foregone in patients with a poor outcome, or in patients with treatment directives. Information on this was not collected in the PRoVENT-COVID study. This explanation, however, seems less likely as there were no differences in any baseline characteristic. The use of NMBA during prone positioning was remarkably lower than in previous studies in the pre-COVID era, in which the incidences were as high as 72%[23] to 88%.[11] It should be noted, though, that recommendations regarding the use of NMBA in ARDS patients[24] may have become obsolete after the publication of the more recent

ROSE trial.[25] Additionally, recommendations for the use of NMBA, as well as the actual use of NMBA during prone positioning, may depend on local practices, and maybe even on the experiences of the healthcare workers that had to take care of patients in the overwhelming first wave of the COVID-19 pandemic. Notably, a recent study in COVID-19 patients showed NMBA use to be associated with a higher risk of and a longer duration of ventilation and longer ICU LOS, even after propensity matching.[26]

A recent study in patients with ARDS due to COVID–19 showed that sustained improvements in oxygenation in response to the first prone positioning session is associated with better outcomes.[27] Recently, the recruitment–to–inflation ratio was suggested as a bedside tool to identify patients that have a high chance of responding well to lung recruitment maneuvers.[28] Unfortunately, we were unable to separate patients based on these approaches, due to the way data were collected.

Prone positioning could come with procedure–related adverse effects.[5, 29] We did not collect these data. It could be hypothesized that the incidence of adverse events during a pandemic is high due to the stressful and demanding situation, with increased workloads and the lack of experienced staff. However, when dedicated prone position teams are present, as was often the case in the centers in the Netherlands early in the pandemic, the rate of procedure–related adverse events could also be low.[30]

The only two factors that had an association with actual use of prone positioning was ARDS severity and FiO_2. This is in line with an earlier observation from before the COVID–19 pandemic.[5] In that study, the major reason for not placing a patient in the prone position was that clinicians deemed hypoxemia not being severe enough. In the current analysis, a PaO_2/FiO_2 ratio < 150 mmHg at two successive observations was used as a cutoff for the indication for prone positioning. This is more strict than in the previous study.

This study has strengths. First, the data were collected in a short time frame during which general care for COVID-19 patients did not change. Second, the study was designed to minimize bias by strictly adhering to a predefined statistical analysis plan. Third, the study involved one-third of all COVID-19 ARDS patients receiving invasive ventilation in the first months of the national outbreak in the Netherlands, and patients were enrolled in 22 ICUs from university-affiliated hospitals, teaching hospitals and non-teaching hospitals, contributing to its generalizability.

PRoVENT-COVID also has limitations. As in any observational study, the knowledge that care data were being captured could have interfered with practice—for instance, doctors and nurses in participating centers could have been keener to use prone positioning. In line with the study design, the use of late prone positioning, i.e., after the first 4 days of invasive ventilation, was not collected. This means that we could not report on the associations of late prone positioning, if that happened, with outcomes. Additionally, it should be realized that reasons to exclude patients

from prone positioning, such as recent tracheal surgery or sternotomy, pregnancy or presence of wounds or burns, were not collected. It is conceivable, though, that these contra-indications were barely present in this cohort. Nevertheless, this may have introduced misclassification bias. The selection of ICUs was based on the personal contacts between steering committee members and ICUs that participated in recent research projects of ventilation, which could have resulted in an over-representation of units with more experience in prone positioning, and therefore a higher incidence. Similar to other epidemiological studies, access to patients' data was restricted to data collectors who were granted access only to patients that were labeled eligible for participation by the local doctors—thus, we could not control whether all COVID-19 patients receiving invasive ventilation in participating ICUs were enrolled. Lastly, the national character of PRoVENT-COVID may make these results not representative for other countries.

The findings of this study extend our understanding of the incidence and practice of prone positioning in patients with ARDS due to COVID–19, and the association of this intervention with outcomes. Our findings may have important suggestions for clinical management.

CONCLUSION

In this national cohort of patients with ARDS due to COVID–19, prone positioning was frequently used, even in patients that did not have an indication for this intervention. Prone positioning may improve outcome of invasively ventilated patients with an indication for this intervention. Factors that had an association with its use were ARDS severity and set FiO_2.

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SUPPLEMENT

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SupplementaryTable S1. Univariable and Multivariable Model of Covariates Selected for Inclusion in the Final Model Mortality

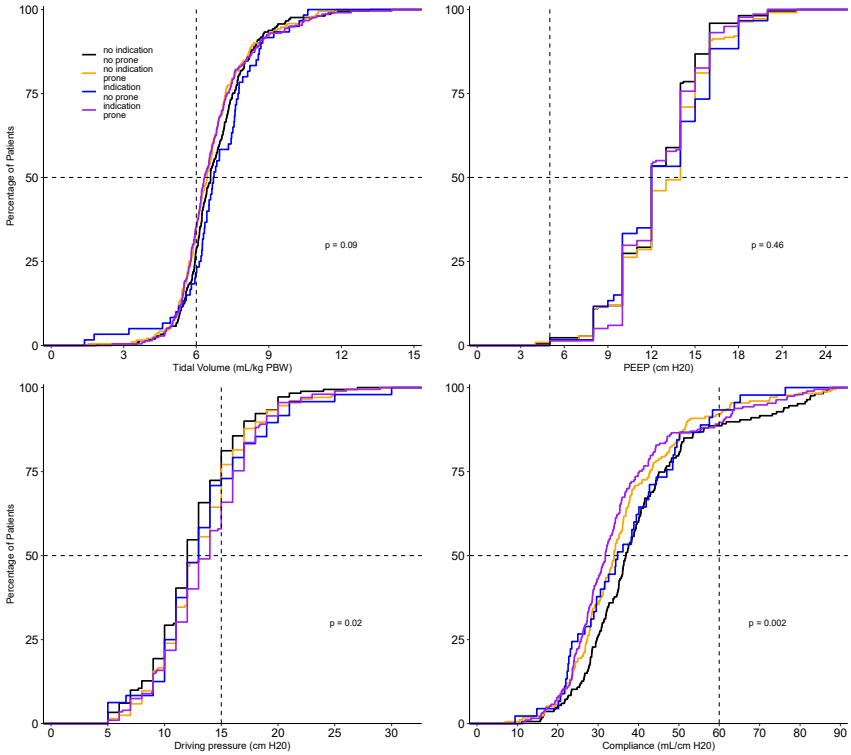
	Univariable Model		Multivariable Model	
	estimates	***p* value**	**estimates**	***p* value**
Covariates				
PEEP	1.08 [0.94 – 1.24]	0.25	-	-
Tidal volume per predicted bodyweight	0.99 [0.86 – 1.14]	0.90	-	-
Severity ARDS	1.12 [0.98 – 1.29]	0.09	0.87 [0.74 – 1.03]	0.11
Body mass index	0.88 [0.76 – 1.05]	0.16	1.12 [0.97 – 1.29]	0.10
FiO_2	1.05 [0.92 – 1.20]	0.43	-	-
NMBA	1.04 [0.79 – 1.35]	0.78	-	-
'Early' prone positioning (day 0 or 1)	0.95 [0.83 – 1.09]	0.52	-	-

Abbreviations: CI, confidence interval; FiO_2, fraction of inspired oxygen; NMBA, neuromuscular blocking agents; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension.
Continuous variables were included after standardization and the hazard ratio represents the increase in one standard deviation of the variable.
Variables with a $P<0.20$ were selected for inclusion in the multivariable model and variables with $P<0.05$ in the multivariable model were selected for inclusion in the final model.

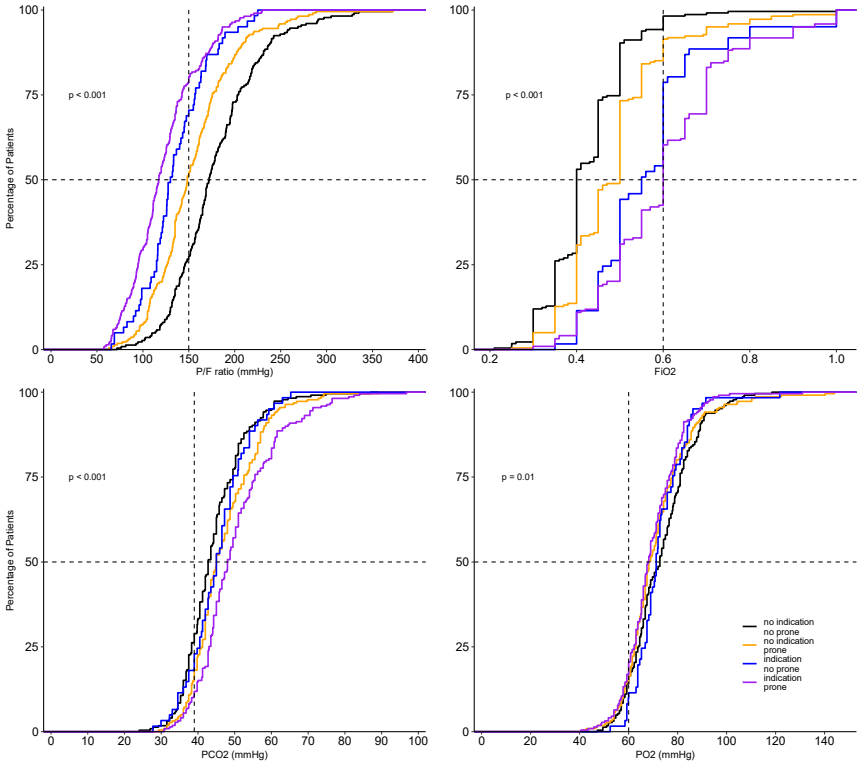
SupplementaryTable S2. Univariable and Multivariable Model linear mixed model initiation prone positioning

	Univariable Model		Multivariable Model	
	Estimates (95% CI)	***p* value**	**Estimates (95% CI)**	***p* value**
Covariates for prone positioning				
PEEP	0.02 [-0.01 – 0.06]	0.16	0.01 [-0.03 – 0.05]	0.54
Severity ARDS	0.11 [0.08 – 0.14]	<0.001	0.08 [0.04 – 0.12]	**<0.001**
Body mass index	0.01 [-0.03 – 0.04]	0.66	-	-
FiO_2	0.09 [0.06 – 0.12]	<0.001	0.07 [0.03 – 0.11]	**0.001**
$PaCO_2$	0.03 [-0.01 – 0.07]	0.11	0.15 [-0.02 – 0.05]	0.42

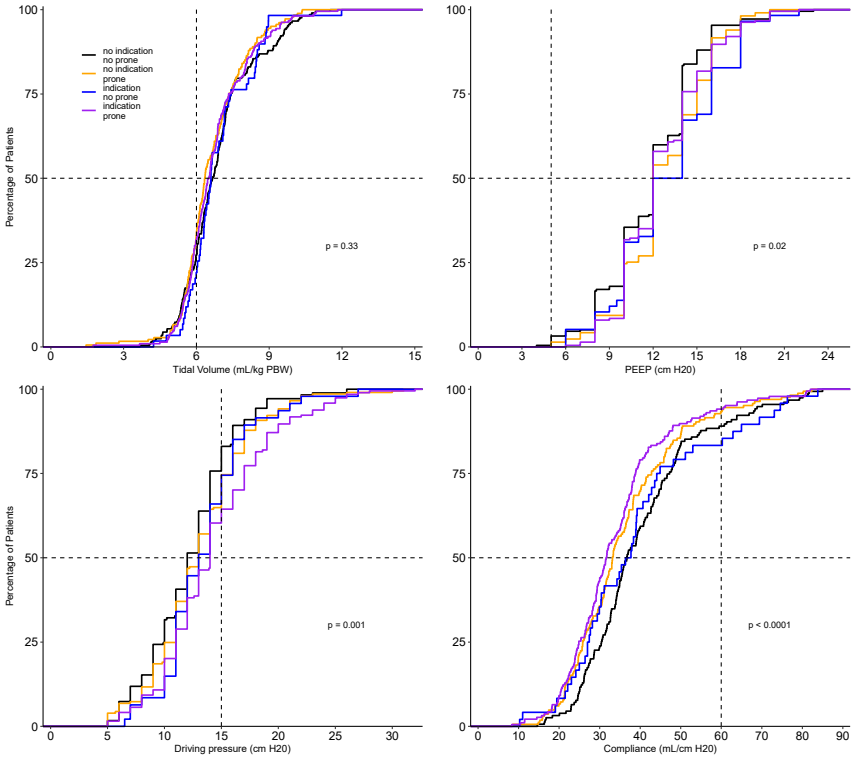
Abbreviations: CI, confidence interval; FiO_2, fraction of inspired oxygen; NMBA, neuromuscular blocking agents; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension.
Continuous variables were included after standardization and the hazard ratio represents the increase in one standard deviation of the variable.
Variables with a $P<0.20$ were selected for inclusion in the multivariable model.



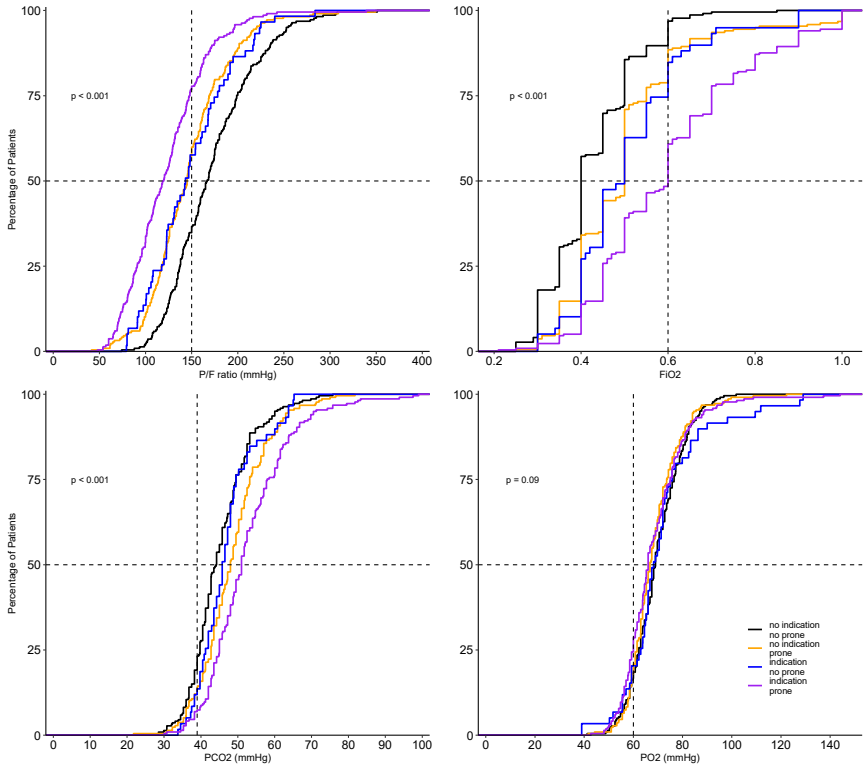
Supplementary Figure S1. Distribution curves 4 groups tidal volume, PEEP, driving pressure and compliance day 1



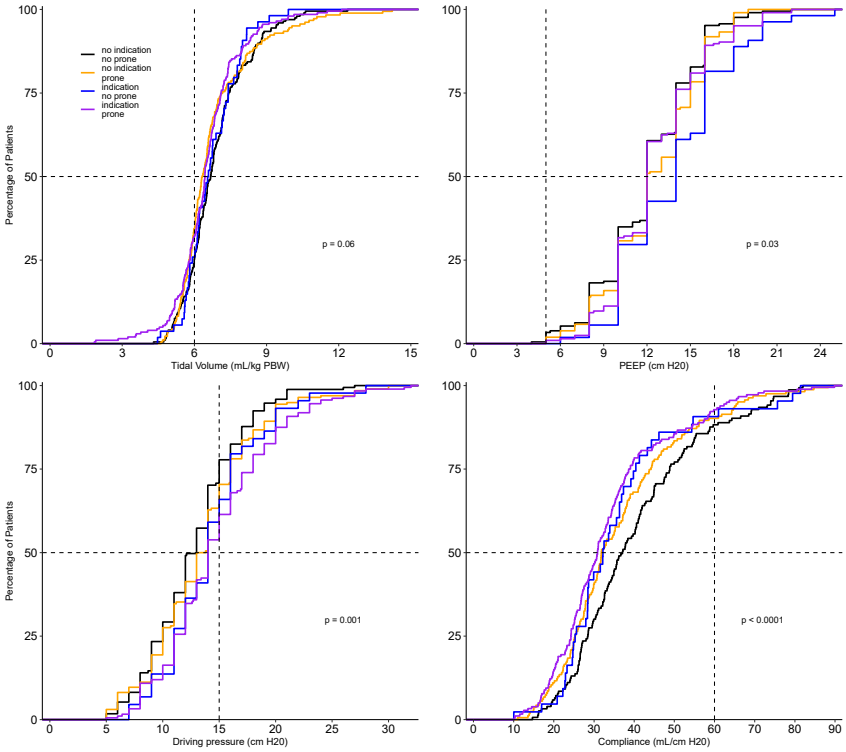
Supplementary Figure S2. Distribution curves 4 groups P/F ratio, FiO_2, PO_2, PCO_2 day 1



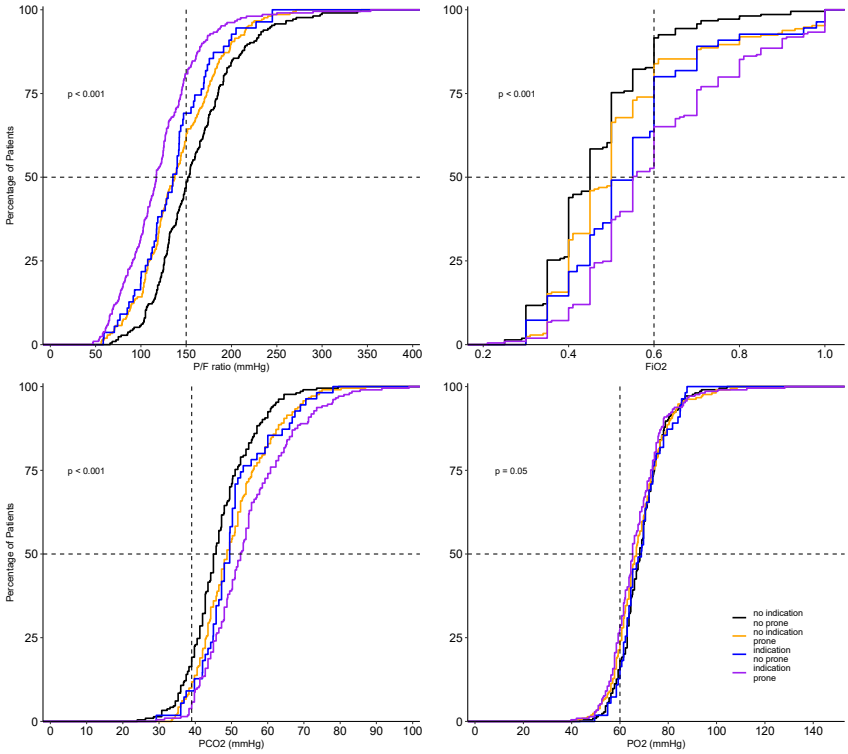
Supplementary Figure S3. Distribution curves 4 groups tidal volume, PEEP, driving pressure and compliance day 2



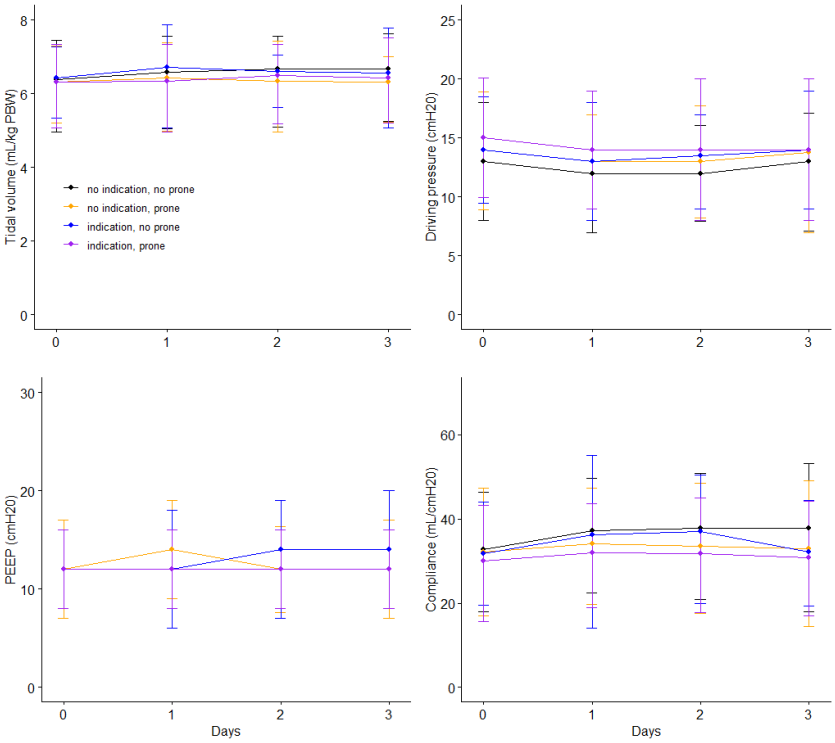
Supplementary Figure S4. Distribution curves 4 groups P/F ratio, FiO_2, PO_2, PCO_2 day 2



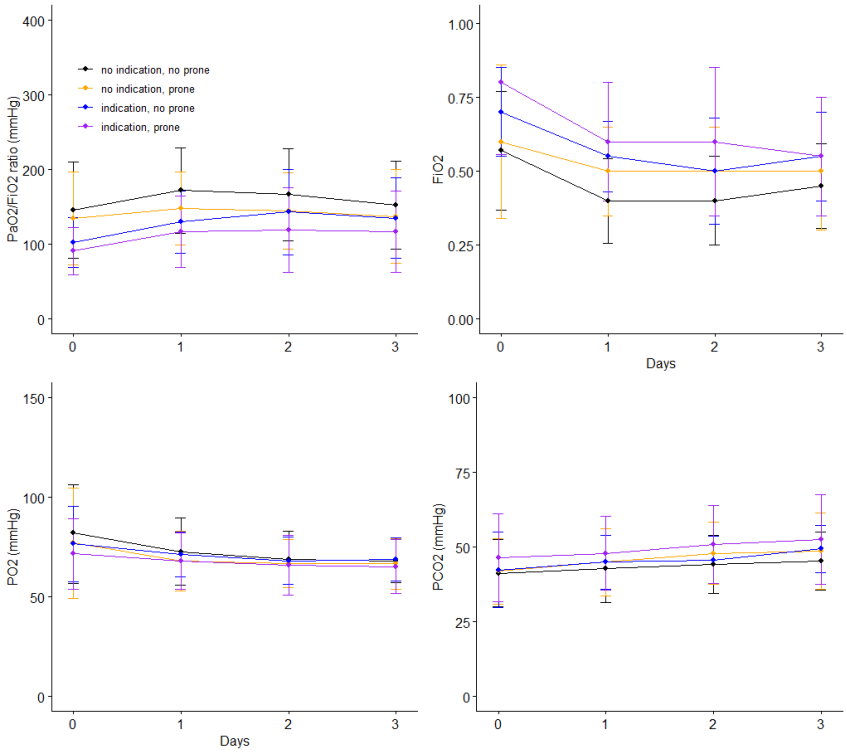
Supplementary Figure S5. Distribution curves 4 groups tidal volume, PEEP, driving pressure and compliance day 3



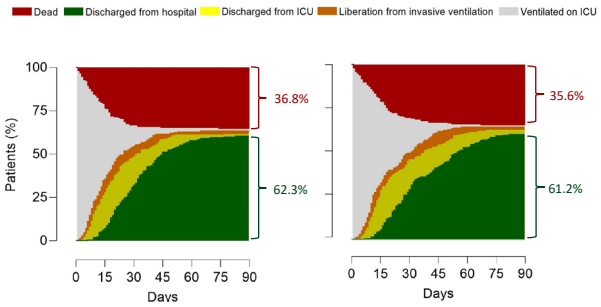
Supplementary Figure S6. Distribution curves 4 groups P/F ratio, FiO_2, PO_2, PCO_2 day 3



Supplementary Figure S7. Line graphs tidal volume, driving pressure, PEEP and compliance day 0, 1, 2, 3



Supplementary Figure S8. Line graphs P/F ratio, PO_2, PCO_2, FiO_2 for day 0, 1, 2, 3



Supplementary Figure S9. Outcomes

Patient outcomes for the groups of patients without an indication for prone positioning, on the left panel patients are displayed that did not receive prone positioning; on the right panel patients are displayed that did receive prone positioning.
HR's for outcomes were (no indication, no prone vs. no indication, prone vs. indication, no prone vs. indication, prone)
28-day mortality: 1.05 [0.76 – 1.45] vs. 0.88 [0.62 – 1.26] vs. 1.15 [0.80 – 1.54] vs. 0.96 [0.73 – 1.26] (P = 0.08)
90-day mortality: 0.93 [0.67 - 1.27] vs. 0.89 [0.64 - 1.24] vs. 1.19 [0.88 - 1.62] vs. 0.99 [0.76 - 1.28] (P = 0.02)
ICU discharge: 1.28 [1.02 – 1.61] vs. 1.03 [0.80 – 1.33] vs. 0.88 [0.69 – 1.12] vs. 0.89 [0.74 – 1.08] (P = 0.02)
Hospital discharge: 1.25 [0.99 – 1.58] vs. 1.07 [0.83 – 1.39] vs. 0.88 [0.69 – 1.13] vs. [0.89 [0.73 – 1.08] (P = 0.01)

Supplementary Table S3. Time dependent cox regression analysis for mortality day 28 and day 90

	Hazard Ratio's (95% CI)	***p* value**
Mortality day 28		0.0027
Indication, no prone	1.46 (0.94 – 2.25)	
Indication, prone	1.20 (0.89 – 1.61)	
No indication, no prone	0.95 (0.70 – 1.27)	
No indication, prone	0.75 (0.55 – 1.02)	
Mortality day 90		0.0075
Indication, no prone	1.56 (1.05 – 2.34)	
Indication, prone	1.22 (0.93 – 1.61)	
No indication, no prone	0.88 (0.67 – 1.72)	
No indication, prone	0.77 (0.58 – 1.02)	

9 Awake proning as an adjunctive therapy for refractory hypoxemia in non-intubated patients with COVID-19 acute respiratory failure—guidance from an international group of healthcare workers

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ABSTRACT

Non-intubated patients with acute respiratory failure due to coronavirus disease 2019 (COVID-19) could benefit from awake proning. Awake proning is an attractive intervention in settings with limited resources, as it comes with no additional costs. However, awake proning remains poorly used, probably because of unfamiliarity and uncertainties regarding potential benefits and practical application.

To summarize evidence for benefit and to develop a set of pragmatic recommendations for awake proning in patients with COVID-19 pneumonia, focusing on settings where resources are limited, international healthcare professionals from high and low- and middle-income countries (LMICs) with known expertise in awake proning were invited to contribute expert advice.

A growing number of observational studies describe the effects of awake proning in patients with COVID-19 pneumonia in whom hypoxemia is refractory to simple measures of supplementary oxygen. Awake proning improves oxygenation in most patients, usually within minutes, and reduces dyspnea and work of breathing. The effects are maintained for up to one hour after turning back to supine, and mostly disappear after 6 to 12 hours. In available studies, awake proning was not associated with a reduction in the rate of intubation for invasive ventilation. Awake proning comes with little complications if properly implemented and monitored. Pragmatic recommendations including indications and contraindications were formulated and adjusted for resource-limited settings.

Awake proning, an adjunctive treatment for hypoxemia refractory to supplemental oxygen seems safe in non-intubated patients with COVID-19 acute respiratory failure. We provide pragmatic recommendations including indications and contraindications for use of awake proning in LMICs.

INTRODUCTION

COVID-19 acute respiratory failure may cause severe hypoxemia.[1] Many patients need to be hospitalized for supplementary oxygen. If this fails, that is, when hypoxemia is refractory to oxygen therapy, invasive ventilation is often needed.

In intubated and invasively ventilated patients with moderate-to-severe acute respiratory distress syndrome, prone positioning can improve oxygenation and has been shown to improve survival.[2,3] Benefit of prone positioning may not be restricted to invasively ventilated patients—at least in theory, non-intubated patients could also benefit from being placed in a prone position.[4,5] So-called 'awake proning' is a cheap intervention, and thus very attractive from an economic viewpoint. Awake proning, however, could be or become uncomfortable if incorrectly performed, especially when it needs to be provided for many hours. It may also come with complications like shoulder injuries,[6,7] pressure ulcers,[8] and aspiration of gastric content.[9]

We invited a group of healthcare professionals with known interest or expertise in awake proning or with practical knowledge regarding care for patients with acute respiratory failure in low- and middle-income countries (LMICs), to develop a set of pragmatic recommendations for use of this intervention—the goal was to develop a guidance, enriched with illustrations for a better understanding and local training of healthcare professionals. Information on awake proning mainly originated in resource-rich settings in high-income countries—the group translated the available information into recommendations for use in resource-restricted settings in LMICs.

METHODS

An international group of healthcare professionals was invited by the study leads (WS, LDB, LP, MJS, FP). Communication and writing within the group and three subgroups was merely by email correspondence and teleconferences, and a central shared online document was used to draft the current guidance.

Several literature searches in Medline were performed, using different combinations of search terms like 'coronavirus disease', 'coronavirus disease 2019', 'COVID-19', and 'SARS-CoV-2', 'prone positioning' and 'awake proning', 'non-intubated', 'non-invasive', 'oxygen therapy', 'high flow nasal oxygen', 'non-invasive ventilation', and 'respiratory monitoring', 'ROX index'. Searches had to be updated several times, as publications continued to appear in the literature during the writing of this report. A final search in Medline was performed in late October, 2020. In addition to these Medline searches, internet searches, mainly through the Google search machine and using the comparable terms were performed to explore the grey literature and search for webinars on awake proning.

Information was bundled and dealt with within three subgroups regarding the following questions: (1) What is the evidence for benefit of awake proning for acute respiratory failure in general, and in COVID-19 pneumonia in particular? (2) What are the recommendations and suggestions for practical application of awake proning for acute respiratory failure in general, and in COVID-19 pneumonia? (3) Should recommendations for use of awake proning differ between high-income countries and LMICs? Members could participate in more than one subgroup, by members' preferences.

Quality of evidence was scored from very high to very low, and the strength of each recommendation was given as strong or weak considering indirectness of evidence and magnitude of effects. For LMICs, the availability, affordability, safety and feasibility of awake proning in patients with acute respiratory failure was used to refine the recommendations if necessary.[10]

RESULTS

Reports from the subgroups – evidence for benefit

The number of studies investigating awake proning is rapidly growing, but thus far randomized clinical trials remain absent. Published studies were heterogeneous with regard to several aspects—for example, supplementary oxygen during awake proning was provided using diverse interfaces, from simple oxygen supplementation via a nasal prong or cannula[11-14] or a Venturi mask,[14] to continuous positive airway pressure (CPAP),[15-18] high flow nasal oxygen (HFNO)[4,12,19,20] and non–invasive ventilation (NIV)[21]; the exact positions taken during awake proning also differed widely; thresholds for awake proning varied, from pulse oximetry as high as > 94%[15,22] to as low as < 90%;[11] duration of awake proning varied too, from 30 minutes to several hours[4,5,11,15,21,23] or even longer;[13,19,20,22,24] and proning could be applied more times per day,[4,5,21] or until low oxygen saturations resolved.[14]

Awake proning improves oxygenation,[4,5,11,12,15,19,25] and also reduces dyspnea.[13,21,22] The improvements in oxygenation are seen within minutes after start of awake proning.[11] The effects of awake proning on oxygenation are maintained for up to one hour after turning back to supine,[15] but disappear after 6 to 12 hours.[12,26] Awake proning also reduces dyspnea sensation and work of breathing by improving ventilation-perfusion.[14,19,21,22,25] Despite this benefit, awake proning is not always tolerated.[5,12,14,21,27]

It remains uncertain whether awake proning can prevent invasive ventilation. Several studies show a low intubation rate with use of awake proning.[12,14,21] Two studies suggest prevention of intubation,[20,22] but this is not confirmed in other investigations in invasively ventilated patients,[15,28,29] nor in patients with severe hypoxemia receiving NIV,[4] nor in patients receiving HFNO.[30] It is highly uncertain whether awake proning can be used as a rescue therapy, that is, to avoid intubation

in patients who already fulfil the criteria for immediate intubation.

It remains unclear whether the effects of awake proning depend on the way supplemental oxygen is administered, albeit that improvements in oxygenation are described with all forms of oxygen supplementation, that is, via nasal cannula or oxygen mask,[11-13,15,19,28,31] CPAP,[15,21] HFNO,[12,20,24,27,30,31] and NIV.[4,21] Some studies suggest that 'early' awake proning (i.e., when oxygen can still be supplied via a simple interface like a nasal cannula)[11,12,22,28] could have a better effect than 'late' awake proning (i.e., when oxygen needs to be supplied via HFNO or CPAP).[15,21,24,32] A change in pulse oximetry readings or respiratory rate induced by awake proning could be useful parameters to define responders versus non-responders. In one study, a rise of SpO_2 > 95% is associated with a lower intubation rate.[28]

Persistent hypoxemia despite supplementary oxygen was used as an indication in all studies, albeit with considerable variation in the degree of hypoxia. Literature remains vague regarding other indications, and also contraindications for awake proning. Based on the studies identified by the searches and consensus within the group, indications and (relative) contraindications for awake proning were formulated (**Table 1**). Consensus was not based on robust evidence, and may depend on various factors such as available resources, and local expertise—for example, in a hospital ward environment with a low nurse-to-patient ratio, it may be challenging to safely use light sedation in the management of a severely dyspneic patient that will receive awake proning.

Reports from the subgroups – practical application of awake proning

Based on the studies identified by the searches and consensus within the group, recommendations and suggestions for practical application of awake proning in COVID-19 patients were formulated (**Table 2**). The group considers it essential to train local teams in correct and safe use of awake proning, especially when light sedation is used. Ideally, an 'awake proning team' consists of two healthcare professionals, including at least one doctor, a nurse or a physical therapist. One professional should provide team leadership. The team will assist the patient to take the correct position, and ascertains continuation of oxygenation supplementation—extra oxygen during positioning could be considered. The healthcare professional should assist in proper positioning of the limbs. Supporting materials, like pillow blocks, cushions or rolled blankets should be closely at hand. To minimize the risks of awake proning a practical checklist or 'proning bundle' can be checked every time a patient is placed in the prone position.[33] (**Table 3**)

For awake proning to be successful, the group thinks motivational support to the patient is one key to success. Prior to proning, why awake proning could work, what it is like to be in a prone position, and how to maintain a proper position, should be explained to the patient and family members if present. A potential increase on pulse oximetry readings and a reduction in dyspnea, coughing

Table 1. Indications and contraindications to apply awake proning

Indications
SpO_2/FiO_2 ratio <315
Acute respiratory failure requiring any supplemental oxygen to maintain saturation > 90%
Able to follow instructions in their native language
Absolute contraindications in the ward and ICU setting
Anticipated difficult airway
Cardiogenic pulmonary edema as cause for respiratory failure
Respiratory rate of above 40/min or accessory muscle use
Unreliable SpO_2 tracing
Immobile or extremely limited mobility
Inability to tolerate proning due to anatomic concerns (e.g. injury or wound on the ventral surface of the body)
Spinal instability
Glaucoma or other condition with acutely elevated intra-ocular pressure
Severe head trauma with high ICP
Absolute contraindications in the ward, but relative contraindication in the ICU setting
Severe oxygenation problems defined as a PaO_2/FiO_2 < 100 mmHg [4] or, alternatively, a SpO_2/FiO_2 < 140 mmHg [60]
Altered mental status or inability to follow commands
Inability to communicate with care team or call for help verbally or with call bell
Hemodynamic instability defined as requiring vasopressor support (i.e. a systolic blood pressure <90 mmHg or mean arterial pressure below 65 mmHg despite appropriate volume resuscitation)
Inability to reposition self for comfort without assistance
Relative contraindications in the ward and ICU setting
Facial injury
Neurological issues (e.g. frequent seizures)
Morbid obesity (BMI> 40)
Pregnancy (2/3rd trimesters)
Pressure ulcers
Concomitant type II respiratory failure, unless chronic, stable and compensated (pH > 7.36). If awake proning is considered it should be trialed and a blood gas taken within 30 minutes to ensure no deterioration in hypercapnia.

BMI: Body Mass Index; FiO_2: oxygen concentration; ICP: Intra Cranial Pressure; PaO_2: arterial blood oxygen concentration; SpO_2: Peripheral oxygen saturation.

Table 2. Recommendations and suggestions for practical application of awake proning in COVID-19 patients (with grading)

	Domain	Recommendation	Grading	Considerations for use in LMICs*
1	Indications	***Suggest:*** consider awake proning in patients with acute respiratory failure requiring supplemental oxygen to maintain saturation > 93%.[11,15,22]	Low quality evidence	Where pulse oximetry is not available, it would be reasonable to trial awake proning for COVID-19 patients with cyanosis, marked tachypnea or other evidence of respiratory distress.
2	Indications	***Suggest:*** consider awake proning in patients able to follow instructions.	Expert opinion	No additional considerations
3	Indications	***Recommend:*** use awake proning during the 1st and 2nd trimester in pregnant women with additional monitoring of the position and the fetus.	Expert opinion	In settings without tocography and doppler, fetal monitoring using clinical auscultation of fetal heart rate should be performed.
4	Contra-indications	***Suggest:*** use awake proning in the 3rd trimester of pregnancy with additional monitoring with caution and on an individual risk-benefit basis.	Expert opinion	In settings without tocography and doppler, fetal monitoring using clinical auscultation of fetal heart rate should be performed.
5	Contra-indications	***Recommend against:*** awake proning in patients with extreme respiratory distress requiring immediate intubation.[15,20,22,28,29]	Low quality evidence	Where mechanical ventilation is not available or affordable, a trial of awake proning may be performed as a rescue maneuver.
6	Contra-indications	***Suggest against:*** awake proning in patients with impaired consciousness.	Low quality evidence	No additional considerations
7	Preparation	***Strongly recommend:*** preparing the patient and the family for what it is like to be in a prone position, what can be expected and how to maintain this position.	Expert opinion	Visual aids may be useful to illustrate the family what will happen. Caregivers will often become a key component of the proning team. Widely available fleece blankets can be used instead of pillows to reduce costs.
8	Preparation	***Recommend:*** preparation for complications (safe airway, suctioning, pressure ulcers).	Expert opinion	Examples of recommended preparations for complications include having the equipment necessary for emergency intubation prepared nearby in case it is required; having a functioning suction machine with a clean suction catheter available at all times ; ensuring careful padding of all pressure areas and daily pressure area surveillance.

Table 2. *Continued*

	Domain	Recommendation	Grading	Considerations for use in LMICs*
9	Monitoring	***Strongly recommend:*** minimum monitoring of pulse rate and peripheral oxygen saturation.	Expert opinion	Where available, a multiparametric monitor or a hand-held or table-top pulse oximeter are preferable to a fingertip pulse oximeter (not easily seen or heard from a distance and may automatically switch off after a certain time period).[61] Whatever device is used, the alarm should be set to alert staff if the SpO_2 drops below 90%. When there are insufficient pulse oximeters available for continuous monitoring, intermittent monitoring should be carried out as frequently as staffing and equipment allow.
10	Monitoring	***Recommend:*** monitoring respiratory rate, work of breathing (use of respiratory muscles) and dyspnea.	Expert opinion	While safety is high, feasibility depends on the local level of staffing. [62]
11	Monitoring	***Suggest:*** possibility of monitoring respiratory status by using the ROX-index.	Expert opinion	Feasibility relies on the availability of pulse-oximetry.
12	Monitoring	***Recommend:*** monitoring of hemodynamic parameters (MAP and SBP).	Expert opinion	We recommend a non-invasive blood pressure measurement at least once an hour where possible (expert opinion).
13	Monitoring	***Suggest:*** visual care monitoring by open wards in event of high surge capacity.	Expert opinion	This is a pragmatic measure that improves patient safety and makes efficient use of staff and PPE.
14	Monitoring	***Suggest against:*** awake proning in conventional hospital wards for patients with severe respiratory failure	Expert opinion	This recommendation may not apply in settings where no higher level of care is available.

Table 2. *Continued*

	Domain	Recommendation	Grading	Considerations for use in LMICs*
15	Oxygen supply	***Recommend:*** use of any available method of oxygen delivery during awake proning.	Expert opinion	Oxygen is a scarce resource in at least one quarter of hospitals in LMICs.[52] The choice between oxygen concentrators, cylinders or centralized systems will depend on local availability and options assessment.[63] Reservoir masks may represent feasible and affordable option. Attention should be paid to ensuring the tubing is not kinked in the prone position and in the case of a reservoir mask that the bag is fully inflated.
16	Oxygen supply	***Suggest:*** use of CPAP or HFNO for delivery of higher FiO_2, depending on the locally available expertise.	Low quality evidence	Availability and affordability of CPAP and HFNO systems is variable but generally low.[64] Feasibility of HFNO is low due to high oxygen demands.
17	Position	***Suggest:*** train multidisciplinary proning teams in approaches on awake and sedated proning with one person having the lead.	Expert opinion	Where insufficient staff are available, care givers can also provide support.[65]
18	Position	***Suggest:*** have a slightly lateral position to turn the face.	Expert opinion	Some patients prefer to keep their head central rather than turned to the side. See figure 2 for a configuration of padding to accommodate this.
19	Position	***Suggest:*** avoid a closed packed shoulder by keeping shoulder of the raised arm around 80 degrees abduction.[35]	Expert opinion	No additional considerations
20	Position	***Suggest:*** full flexion of knees if possible and maximum range ankle motion.	Expert opinion	Extra pillows may be needed. Widely available fleece blankets can be used instead of pillows to reduce costs.
21	Position	***Suggest:*** use analgesia when low back pain becomes a problem.	Expert opinion	
22	Position	***Recommend:*** supportive padding above and below the gravid uterus when pregnant women are proned (Figure 1).	Expert opinion	Folded fleece blankets can be used for this purpose.

Table 2. *Continued*

	Domain	Recommendation	Grading	Considerations for use in LMICs*
23	Position	***Suggest:*** a semi-lateral prone position in pregnant woman in the 2nd/3rd trimester as an alternative (Figure 1).	Expert opinion	No additional recommendations
24	Hydration and nutrition	***Recommend:*** maintain normovolemia.	Expert opinion	No additional recommendations
25	Hydration and nutrition	***Suggest:*** allow oral intake unless there is a high risk of intubation.	Expert opinion	No additional recommendations
26	Hydration and nutrition	***Suggest:*** stay in supine position for one hour after oral feeding in supine position.	Expert opinion	No additional recommendations
27	Risk management	***Recommend:*** have equipment for endotracheal intubation nearby and frequently checked.	Expert opinion	This only applies to centers where mechanical ventilation is available.
28	Risk management	***Recommend:*** have an intravenous port available for sudden clinical deterioration.	Expert opinion	No additional recommendations
29	Risk management	***Recommend:*** have materials for (endotracheal or nasal) suctioning standby.	Expert opinion	Where electrical suction devices are not available, a manual suction pump or bulb suction can be used.
30	Risk management	***Suggest:*** start reverse CPR until a team is ready to get the patient in supine position.	Expert opinion	CPR should only be commenced once staff attending the patient are wearing N95 respirators/ masks or equivalent.

*Considerations regarding feasibility, availability, safety and affordability.[10]
Abbreviations: CPAP: Continuous Positive Airway Pressure; CPR: Cardiopulmonary resuscitation; HFNO: high flow nasal oxygen; MAP: mean arterial pressure; NIV: non-invasive ventilation; PPE: Personal Protective Equipment; SBP: systolic blood pressure

Table 3. Safe awake proning checklist

Preparation	**Proning**	**After turning/during proning**
Patient	***Patient***	***Patient***
Identity Explanation procedure Document duration of procedure Consent	Self-proning Assisted proning	Comfort Document chosen position (prone, lateral) Document position of arms
Materials	***Materials***	***Materials***
Pillows, slide sheet Crash cart Oxygen available Suction equipment available Monitoring: pulse-oximetry if available	Sufficient room between the head and shoulders for oxygen supply In pregnant women special attention to alleviate pressure on the gravid uterus	Provide emergency buzzer, mobile phone, improvised rattle
Check		***Check***
Vital signs: SpO_2, RR, HR, BP IV access Nurse call system Baby monitor in case of pregnancy	Oxygen supply continued	Vital signs: SpO_2, RR, HR, BP IV access Nurse call system Additional external fetal monitoring
		Medication
		Pain: paracetamol 4 dd 1 g Anxiety: low dose benzodiazepine Oxazepam 10 mg po Midazolam 1-2 mg po
Emergencies:	***Emergencies:***	***Emergencies:***
Emergency team for supine position Crash cart (intubation equipment) available	Emergency team for supine position Crash cart (intubation equipment) available	Emergency team for supine position Crash cart (intubation equipment) available and know where to find

Based on WHO surgical checklist and Safe prone checklist [66]
BP: blood pressure; HR: heart rate, IV: intra venous, RR: respiratory rate, SpO_2: peripheral oxygen saturation

and sputum production could increase following the position change—this is usually short-lasting. It can be useful to know if the patient normally sleeps face down (e.g., prone), to adjust this information. Patients could find awake proning uncomfortable, but this may be mitigated through supportive nursing care, and noticing the marked improvements of pulse oximetry readings. Family can stay with patients who are proning, and use of mobile devices to spent time and communicate with relatives should be stimulated. If use of sedatives or anxiolytics is being considered to facilitate prone positioning in non-intubated patients, this should be undertaken in a closely monitored location, with access to continuous oxygen saturation, blood pressure and electro-cardiogram monitoring. Pain medication could be considered, as pain related to stiffness of shoulders and neck could develop.

Frequent assessment for tolerability, at least within ten minutes after start of proning is considered important. In some patients it may be necessary to start a benzodiazepine, clonidine, or dexmedetomidine, but only if the setting allows—also morphine, in low dosages, could be useful in a severely dyspneic patient. In those cases, proper monitoring, including continuous or intermittent pulse oximetry, blood pressure and maybe electrocardiogram (EKG) could be useful.

The vast majority of patients will receive supplemental oxygen through interfaces like a nasal prong or cannula, a face mask, CPAP via a masks or a ventilation hood, HFNO or NIV.[15-17,19] There is no evidence as to which interface is best in patients who receive prone positioning. Nasal interfaces and masks seem more practical and better tolerated than hoods,[5] especially in elderly patients.[15] One current multicenter randomized clinical trial is testing the efficacy of different interfaces for supplemental oxygen during awake proning in patients with COVID-19 acute respiratory failure.[34]

In patients with mild hypoxemia 'self-proning' could be possible, eventually with help of a family member. In patients with severe hypoxemia, 'assisted proning' is likely to be superior to 'self-proning', as patients may need all of their energy to breathe, and thus need help—assistance also prevents dislocation of the interfaces for supplemental oxygen and any indwelling catheter. Assistance may prevent an increase in oxygen consumption induced by changing the position, especially in older, frail, pregnant and obese patients.

Some refinements could increase safety of awake proning and may allow acceptance for a longer period of time. Suggested positions are illustrated in **figures 1** and **2**. A slightly lateral prone position allows a patient turn the face to one side, which can be supported by a pillow or rolled blanket placed under one side of the chest, and a raised arm embracing the pillow (the 'front crawl' or 'swimmers position'). While in the prone position, the patient faces the armpit of the raised arm of which the elbow is flexed at ~ 90 degrees, while the contralateral arm remains aligned with the body. A maximum closed packed

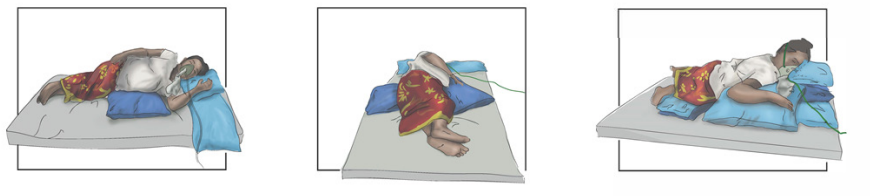

Figure 1. Awake proning in a 9 month pregnant woman. Both ¾ prone and full prone options are shown. Suggested position is an indication and could be adapted based on patient preferences. *Drawing Marco Rosetti.*

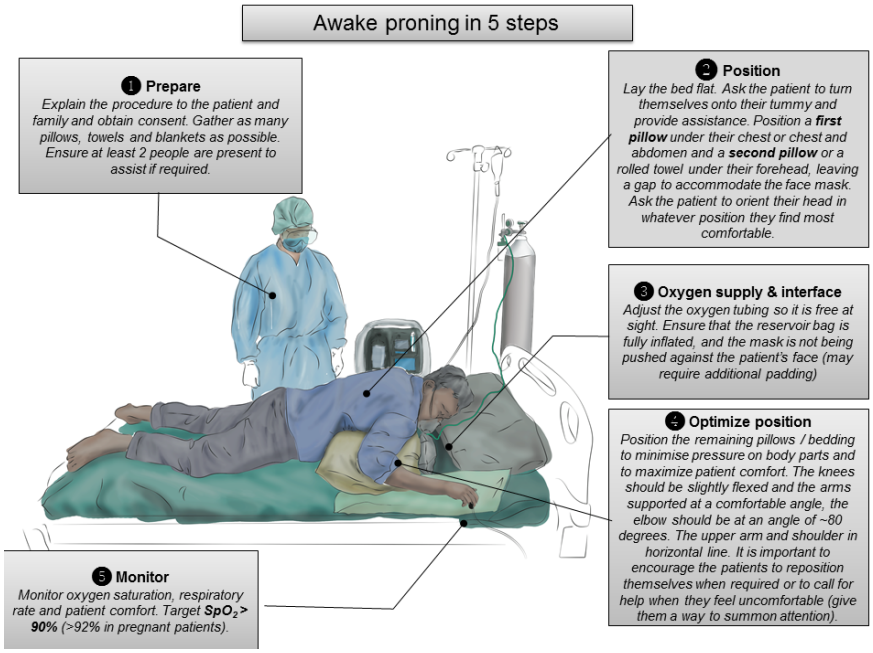

Figure 2. Visual aid to facilitate awake proning implementation in a resource limited setting. Suggested position is an indication and could be adapted based on patient preferences. Adapted with permission from a prone positioning checklist developed in Laos.[67] *Drawing Marco Rosetti.*

position of the shoulder is avoided by keeping the shoulder of the raised arm at ~ 80 degrees abduction, or even lower if possible.[35] The upper arm and shoulder blade are positioned in a straight horizontal line to protect the shoulder, and arm repositioning is encouraged, if pain or stiffness occurs. Slight adjustments or repositioning of the legs and hip should be encouraged to prevent pressure ulcers and meralgia paresthetica. The latter complication is a result of compression injury of the lateral femoral cutaneous nerve.[36] The side of the swimmers position changes frequently, preferably every two or three hours. Full flexion of the knees should be possible, with a maximum range of ankle motion to prevent stiffness

and pointed feet. In patients with lower-back pain, a semi-prone, or lateral position could be taken. If this does not provide relief the lower-back pain, pain medication could be considered.

As patients in prone position may need urgent intubation, they should remain fasting. Fasting is also advisable because of an increased risk for aspiration when in a prone position. Patients should thus be encouraged to take oral feeds in supine, head-up position, between the sessions, if allowed, and should not be placed in a prone position for at least one hour after oral intake. Fluids should be given intravenously, if needed. However, sips of water could be taken with the bed in a more upright position.

Direct visual care and monitoring of patients during awake proning is facilitated by designated areas for cohorts of patients. Monitoring of respiratory rate, accessory muscle use and work of breathing could help identifying patients who need escalation of care. The ratio of oxygen saturation (ROX) index,[37] defined as the ratio of SpO_2/FiO_2 to respiratory rate (RR), has been proposed for monitoring. This index combines three parameters that assess a patient's respiratory status. Improvement in the ROX index during awake proning could indicate a lesser likelihood for intubation,[38] but experience with the ROX index in patients with COVID-19 acute respiratory failure is still very limited.

In case of cardiac arrest in a prone position, 'reverse CPR'[39,40] can and must be started until a team is available to turn the patient back to supine.[41] This team should be identified and always be readily available. Emergency endotracheal intubation equipment and materials must be close by and regularly checked for immediate use alongside relevant emergency drugs.

Finally, the group suggests awake proning should not be withheld in pregnant patients,[42-47] but supplemental oxygen should be provided such that pulse oximetry remains ≥ 95%.[43] To prevent aortocaval compression in pregnant patients,[48] additional measures can be taken by organizing extra pillows and monitoring.

Reports from the subgroups – recommendations for awake proning in LMICs

As awake proning does not require particular resources, it should be considered in hypoxemic patients with COVID-19 acute respiratory failure that do not respond to simple supplementary oxygen in settings where resources are limited. The group considers awake proning with any available method of respiratory support a safe intervention, also in LIMCs. Awake proning may prevent the need for invasive ventilation which is important for settings with limited numbers of ventilators.[14,32] In fact, at times awake proning may be the only option to improve oxygenation in settings. Limitations regarding awake proning in LMICs include a lack of human resources, training, and challenges with infrastructure and equipment.[49]

The group recognizes the limitation of staffing in many LMICs, and that a

'proning team' may not always be feasible. The guidance by one trained healthcare professional–or two in an obese or a non-cooperative patient, however, is seen as one minimal requirement to proceed with this intervention. It is always important that a patient can be turned supine with urgency to allow emergency procedures such as CPR. Training of staff becomes pivotal in limited-resource settings, as it is possible to spare time and resources when exact maneuvers are known by the team. **Figures 1** and **2** provide additional training material.

Oxygen is listed as an essential medication by the World Health Organization[50] but remains a very limited resource in many settings.[51-53] Low-flow supplemental oxygen via nasal prongs, sponge-tipped catheters or face masks are increasingly available and affordable, although one quarter of hospitals surveyed in a LMICs study reported gaps in oxygen supply.[52] Facemasks with reservoir allow increasing the FiO_2 significantly and should be strongly considered (**Figure 2**). HFNO and NIV are feasible in LMICs, but not widely available. They come at additional costs for the interfaces and devices. They also come with technical challenges and practical concerns, as they depend on a reliable source of oxygen and electricity. CPAP and HFNO apparatuses may rapidly use up oxygen supplies—indeed, HFNO consumes oxygen at over four times the rate of low flow oxygen support, and typically HFNO may consume the entire content of a large oxygen cylinder within 2 to 3 hours, rapidly depleting oxygen supply.

Close monitoring and clear escalation criteria are needed with awake proning, also in resource-limited settings. In LMICs, pulse oximeters are often not available, but recent initiatives have been set up to provide them on a larger scale.[54] Pulse oximetry together with monitoring of clinical and vital signs might help timely identification of those patients who need escalation of care.[55] In settings where blood gas analyzers are unavailable, the SpO_2 relative to inspiratory oxygen concentration, or SpO_2/FiO_2 ratio, can be used for continuous monitoring, decision-making and prognostication.[56-58] The ROX index is likely to be useful because it requires simple input (SpO_2/FiO_2 and respiratory rate) and is easy to calculate at the bedside.[59]

During the supine periods between awake proning, oral intake is to be encouraged to maintain normovolemia in resource-limited settings, as other resources for fluid intake are usually limited. The risk of aspiration, however, should be highlighted, especially in obese patients. The suggestion of using low dose benzodiazepines or morphine to enhance awake proning should be conducted with care in environments with limited or absent patient monitoring.

DISCUSSION

A rapidly growing number of observational studies describe use of awake proning in patients with COVID-19 acute respiratory failure in whom hypoxemia is refractory

to simple supplementary oxygen. Awake proning improves oxygenation within minutes and the effects are maintained for up to one hour after turning back to supine and disappear mostly after 6 to 12 hours. Awake proning is associated with few complications. Since no particular technological resources are required it is particularly applicable in settings where resources are limited, or even absent. A set of pragmatic recommendations were formulated on awake proning in relation to indications and contraindications, oxygen supply, position, nutrition, monitoring and risk management based on the available evidence and experiences of health care workers in LMICs.

It is important to notice that so far there is no randomized trial evidence for the effect of awake proning in patients with COVID-19 acute respiratory failure. Current evidence comes from few studies, mostly case reports and single-center observations. None of these originated in LMICs. The available results, however, suggest that awake proning could be effective adjunctive therapy, that is also safe and tolerable. The suggestion that it may prevent the need for invasive ventilation or increased need of oxygen makes this intervention worth a try, certainly in settings where there is a shortage of ventilators or where ventilators are absent[20,22] or healthcare is unaffordable for patients.

One strength of this guidance on awake proning is the cooperation of a set of healthcare workers from resource-rich settings in high-income countries and from resource-limited settings in LMICs. There was a large expertise in proning, and a deep understanding of the challenges in ICUs in LIMCs. Also, the group consisted of various types of healthcare workers, including (ICU) doctors, (ICU) nurses, and physiotherapists.

This work also has limitations. We emphasize that this is not a systematic review, but rather a clinical appraisal of the available literature and personal clinical experiences of healthcare workers in various settings around the world. We cannot exclude selection and information bias.

CONCLUSION

Awake proning is an attractive and safe adjunctive treatment for hypoxemia refractory to supplemental oxygen in patients with COVID-19 acute respiratory failure, especially in settings where there is shortage or absolute lack of ventilators. Here, this could be the only option to improve oxygenation. It may even prevent the need for invasive ventilation, although randomized trial evidence remains lacking—randomized clinical trials are urgently needed.

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10 Practice of awake prone positioning in critically ill COVID–19 patients—insights from the PRoAcT–COVID study

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ABSTRACT

We describe the incidence, practice and associations with outcomes of awake prone positioning in patients with acute hypoxemic respiratory failure due to coronavirus disease 2019 (COVID–19) in a national multicenter observational cohort study performed in 16 intensive care units in the Netherlands (PRoAcT-COVID-study). Patients were categorized in two groups, based on received treatment of awake prone positioning. The primary endpoint was practice of prone positioning. Secondary endpoint was 'treatment failure', a composite of intubation for invasive ventilation and death before day 28. We used propensity matching to control for observed confounding factors. In 546 patients, awake prone positioning was used in 88 (16.1%) patients. Prone positioning started within median 1 [0 to 2] days after ICU admission, sessions summed up to median 12.0 [8.4–14.5] hours for median 1.0 day. In the unmatched analysis (HR, 1.80 [1.41–2.31]; $p < 0.001$), but not in the matched analysis (HR, 1.17 [0.87–1.59]; $p = 0.30$), treatment failure occurred more often in patients that received prone positioning. The findings of this study are that awake prone positioning was used in one in six COVID–19 patients. Prone positioning started early and sessions lasted long but was often discontinued because of need for intubation.

INTRODUCTION

Patients with severe coronavirus disease 2019 (COVID–19) can develop profound hypoxemia that is refractory to low–flow and even high–flow oxygen supplementation.[1] Prone position has been shown to improve outcomes in ventilated ARDS patients.[2] Several changes, induced by prone positioning, could be responsible for this benefit.[3] First, in a prone position the heart is no longer causing atelectasis because of the changed position in the thorax. Additionally, the chest wall compliance changes and there is a more even distribution of aeration when turning a patient prone. The latter is associated with a better ventilation-perfusion ratio. This all allows changes in ventilator setting, specifically those that are associated with ventilator-induced lung injury. Last but not least, prone position could reduce the afterload of the right ventricle, and with prone position the direction of the trachea is downward, which could help sputum evacuation.

The use of prone positioning in non-intubated patients, so called awake prone positioning, was initially reported in case series to improve oxygenation in patients with COVID-19.[4] Additionally, cohort studies showed the potential to improve outcomes in patients with acute hypoxemic respiratory failure due to COVID-19.[5,6] One randomized clinical trial reported an improved outcome with the use of awake prone positioning in patients with respiratory failure due to COVID-19.[7] Another randomized clinical trial did show a lower intubation rate, but failed to show a difference in mortality.[8]

Based on available literature and clinical experience, practical guidelines for prone positioning of non–intubated patients became rapidly available after the initial wave of the pandemic.[9-12] Since then, use of awake prone positioning has increased However, results on practical aspects of awake prone positioning in patients after admission to the intensive care unit (ICU), as well as its relation with clinical outcomes, are relatively scarce.[5-7]

How frequent awake prone positioning was used in the ICU during the second wave of the national outbreak in the Netherlands, which occurred after the change in the guidelines, is unknown. It is also uncertain how it was applied and whether it was associated with patient characteristics and outcome. Therefore, we analyzed the database of a large observational study, named 'Practice of Adjunctive Treatments in ICU Patients with COVID–19' (PRoAcT–COVID).[13]

The primary aim was to determine the practice of prone positioning in patients that did not immediately proceed with invasive ventilation after arrival in the ICU. The second aim was to compare epidemiology and outcomes in patients that received prone positioning versus patients that received standard care. We hypothesized that prone positioning was used often, and that its use had associations with outcome.

MATERIALS AND METHODS

Study design

PRoAcT–COVID is an observational cohort study in critically ill patients with COVID–19 that were admitted to ICUs of the participating hospitals in the Netherlands. In PRoAcT–COVID, we captured data in the first 3 months of the second wave of the national outbreak regarding pharmacological and non–pharmacological interventions. The protocol was approved by the local Institutional Review Board of the Amsterdam University Medical Centers, location 'AMC' (W20_526 # 20.583), and thereafter in all participating centers. Need for individual patient informed consent was waived seen the observational nature of the study. The study plan and the analysis plan for this current analysis were both pre–published.[13,14] PRoAcT–COVID is registered at clinicaltrials.gov with trial number NCT04719182. Registered 22 January 2021.

Patients

We screened patients that were admitted to the ICUs between October 2020 and January 2021 on admission day. Inclusion criterium was an admission to the ICU for acute hypoxemic respiratory failure due to RT–PCR confirmed COVID–19. Acute respiratory failure was defined as the need for hypoxemia refractory to oxygen supplementation with low flow oxygen systems, like nasal prong or simple face masks. Patients aged < 18 years and patients with an alternative diagnosis were excluded.

For the current preplanned descriptive analysis of the PRoAcT-COVID study we excluded patients that were under invasive ventilation at ICU admission or intubated immediately; immediate intubation was defined as intubation that happened within the first 2 hours after arrival in the ICU. We also excluded patients that were transferred from or to ICUs from other non–participating hospitals within the first 2 calendar days of ICU admission. This was done because of two reasons: first, we were not allowed to capture data of patients in the non–participating centers: second, we could not exclude the possibility that an imminent transport to another ICU may have influenced decisions to intubate the patient. At the time of this study, scheduling was chaotic, often not knowing exactly when a patient would be transported and patients frequently had to be moved within one or two hours. Since the policy was to transfer a patient only when intubated, this meant that patients were frequently intubated while awaiting transport.

Collected data

We collected baseline and demographic variables, including sex, age, weight and height, major comorbidities, and home medication, the first day with symptoms, the day of the definite diagnosis of COVID–19, the day of hospital and ICU

admission. The day of ICU admission, which in theory could last from 1 min to 23 h and 59 min, was named 'day 0'. Successive days were named 'day 1', 'day 2' onwards to 'day 28'. The Simplified Acute Physiology Score (SAPS) II was calculated at 24 hours after ICU admission[15] and extracted from routinely captures and in part automatically generated data in the patient data management systems as present in the participating ICU.

We collected data regarding prone positioning, including time of initiation, the number of sessions per day, and the number of days it was continued. The data collectors were trained to collect data on prone positioning from the data patient management system, wherein body position is always reported. This was further confirmed by reading each nursing report. This allowed us to determine whether a patient ever was placed in a prone position, and also the timing of the intervention. We also collected detailed information regarding oxygen support until 28 days or ICU discharge, including the type of oxygen interface, i.e., nasal sprong or cannula, non–rebreather mask or Venturi mask, continuous positive airway pressure (CPAP), high–flow nasal oxygen (HFNO), and noninvasive and invasive ventilation.

Up to day 28, we captured intubation status, mortality and date of ICU and hospital discharge.

Patient classification

To describe current practice of awake prone positioning we classified patients into two groups. The group of patients that were placed in the prone position, hereafter named the 'prone positioning group', were compared to the group of patients that were not placed in prone position, hereafter named the 'standard care group'.

Endpoints

The primary endpoint was the practice of awake prone positioning, including the following aspects: timing, duration of prone sessions, frequency, and for how long prone positioning sessions were repeated. One secondary endpoint was 'treatment failure', a composite endpoint of intubation or death before day 28—this endpoint was used in a meta–trial of awake prone positioning in patient with acute hypoxemic respiratory failure due to COVID–19.[7] We also report the two components separately, as well as ICU and hospital length of stay, and ICU and hospital mortality.

Power calculation

Since this is a preplanned descriptive analysis of an observational cohort study, we performed no a priori sample size calculation; the number of patients admitted in the participating centers served as the convenience sample.

Statistical analyses

Categorical variables are presented as counts (frequencies), and continuous variables are presented as medians (interquartile ranges [IQRs]). Independent categorical variables were compared with Fisher exact test, and continuous variables with Wilcoxon rank–sum test.

The incidence of awake prone positioning is expressed as the proportion of patients that was admitted to the ICU not yet intubated and not intubated early after ICU admission. Timing of prone positioning is expressed as the number of days between ICU admission and start of the first session of awake prone positioning. Duration of prone positioning is expressed as the mean number of hours of each session. Frequency is expressed by the number of sessions per days a patient received awake prone positioning. Continuation of prone positioning is expressed as the number of days a patient received one or more awake prone positioning sessions. Types of oxygen support used at the day of initiation of awake prone positioning and thereafter are reported for the awake prone positioning group. The endpoint treatment failure, and its two components, are visualized using Kaplan-Meier curves, as were the endpoints length of stay in ICU and hospital.

Since the exposure was not randomly assigned, we also performed a propensity matched analysis to control for known confounders. This approach was chosen to account for the fact that the exposure to the intervention of interest might not occur during the study if improvement occurs or termination of efforts, e.g., because of intubation or death, occurred first. The propensity score was calculated by means of a generalized linear model based on a (shared-frailty) Cox proportional hazards model with exposure during follow–up as the dependent variable and based on baseline characteristics and daily information. The following baseline variables were included based on clinical relevance: age; gender; and body mass index (BMI). In addition, the following covariate assessed daily was included: PaO_2. The propensity score for each patient was then derived from the Cox model as the hazard component (i.e., the linear predictor) at any given moment from the model. A 1:3 risk set matching on the propensity score was performed using a nearest neighbor–matching algorithm with a maximum caliper of 0.01 of the propensity score. A strict margin of the maximum caliper of the propensity score was chosen to match patients. With this, some patients may not be matchable, resulting in a lower number of patients in the matched analysis. Patients receiving the intervention at any given moment were separately and sequentially propensity score matched with a patient who was at risk of receiving the intervention within the same moment. At–risk patients included those who were still undergoing treatment and did not receive the intervention before or within the same moment. At–risk patients therefore also included patients who received the intervention later, as the matching should not be dependent on future events.[16] As such, the matched group with no intervention includes patients who subsequently received

the treatment (although later than their matched counterpart). In all analyses, the time–dependent exposure was considered a stochastic process (counting process) that equals zero from time 0 until exposure, then it equals to one until the end of observation. This provided a correction for the possibility of immortal time bias. The performance of matching was assessed through standardized differences between baseline characteristics.

Binary outcomes will be compared with mixed–effect generalized linear models with binomial distribution and expressed as odds ratio and 95% confidence interval (CI). Continuous outcomes will be compared with mixed–effect generalized linear models with Gaussian distribution and expressed as mean difference and 95% CI. Time–to–event outcomes were assessed with shared–frailty Cox proportional hazard models. ICU length of stay will be analyzed with a clustered Fine–Gray competing risk model with death before the event as competing risk. In all models the hospitals will be included as random effect to account for potential clustering. Wherever appropriate, Kaplan–Meier curves are used to present time–to–event outcomes. All tests were 2–sided, with a significance level set at < 0.05. All statistical analyses were conducted using R v.4.0.3 (R Foundation for Statistical Computing: Vienna, Austria).

RESULTS

Patients enrolled

16 ICUs from various types of hospitals, including academic, teaching and non–teaching hospitals participated in PRoAcT–COVID, and a total of 946 patients were enrolled. Of these, 546 patients were eligible for this preplanned descriptive analysis. Main reason for exclusion was admission under invasive ventilation or immediate intubation after ICU admission (**Figure 1**).

Most patients were male, and were overweight or obese. Patients were severely ill, as reflected by high disease severity scores, and had severe hypoxemia despite high levels of FiO_2 that was often supplied by means of HFNO. After hospital admission, patients were admitted to the ICU within one or two days (**Table 1**).

Practice of awake prone positioning

Awake prone positioning was used in 88 (16.1%) patients. Patients were placed in a prone position median 1 [0 to 2] days after ICU admission. Total time of awake prone positioning summed up to median 12.0 [8.4–14.5] hours for median 1.0 day. HFNO was the most often used oxygen interface during awake prone positioning (79.5%), followed by CPAP (9.1%) (**Table 2**).

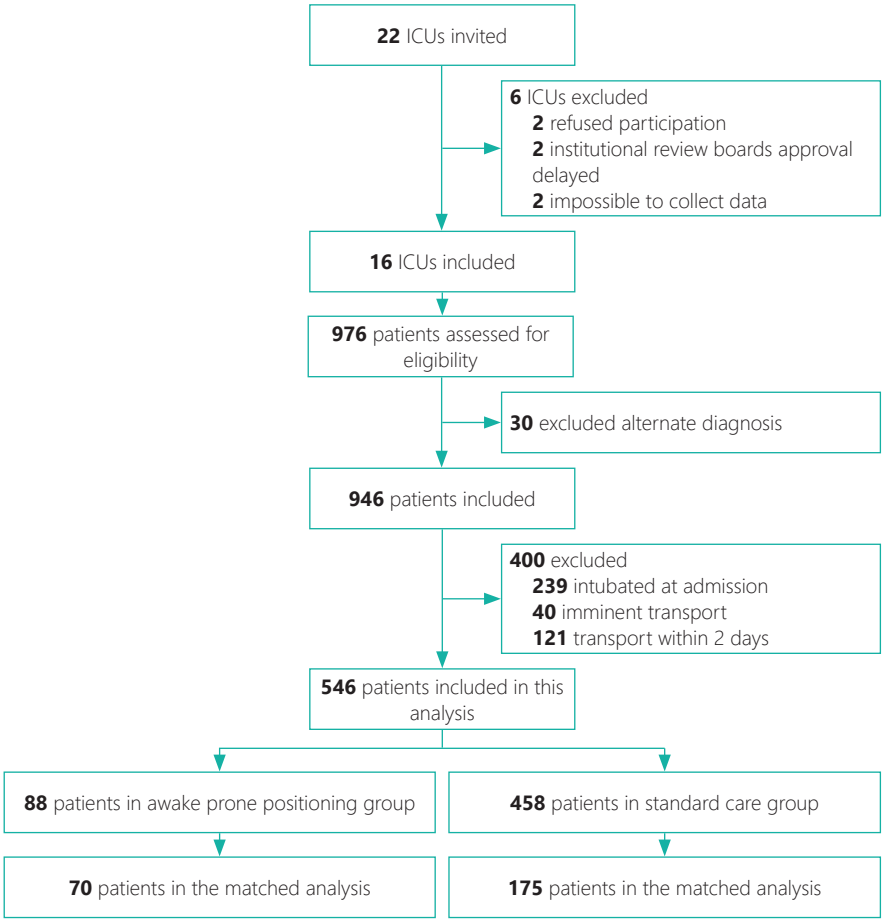

Figure 1. Flow chart of patient inclusion

Table 1. Baseline characteristics

	Overall N = 546	Prone Positioning N = 88	Standard Care N = 458	*P*
Age, years (median [IQR])	67 [59 - 73]	66 [60 - 73]	67 [59 - 73]	0.946
Male gender, N (%)	402 (73.6)	60 (68.2)	342 (74.7)	0.257
BMI, kg/m2 (median [IQR])	28.0 [25.3 - 31.8]	28.8 [25.7 - 31.9]	27.9 [25.2 - 31.8]	0.543
SAPS II score (median [IQR])	43 [33 - 53]	47 [37 - 53]	43 [32 - 53]	0.056
Do-not-intubate order, N (%)	31 (5.7)	2 (2.3)	29 (6.3)	0.209
Comorbidities				
Arterial hypertension, N (%)	219 (40.1)	39 (44.3)	180 (39.3)	0.447
Cardiovascular disease, N (%)	135 (24.7)	14 (15.9)	121 (26.4)	0.050
Heart failure, N (%)	30 (5.5)	2 (2.3)	28 (6.1)	0.233
COPD or asthma, N (%)	97 (17.8)	16 (18.2)	81 (17.7)	1.000
Diabetes mellitus, N (%)	178 (32.6)	24 (27.3)	154 (33.6)	0.298
Chronic kidney disease, N (%)	50 (9.2)	7 (8.0)	43 (9.4)	0.822
Malignancy, N (%)	39 (7.1)	6 (6.8)	33 (7.2)	1.000
Neuromuscular disease, N (%)	13 (2.4)	2 (2.3)	11 (2.4)	1.000
Obstructive sleep apnea, N (%)	39 (7.1)	6 (6.8)	33 (7.2)	1.000
Days in hospital before ICU admission, (median [IQR])	1.0 [0.0 – 4.0]	2.0 [0.0 – 3.0]	1.0 [0.0 – 4.0]	0.085

Abbreviations: BMI: Body Mass Index; SAPS: Simplified Acute Physiology Score; COPD: Chronic obstructive pulmonary disease and/or asthma.

Table 2. Oxygen supplementation at start of prone positioning

	Prone Positioning N = 88
HFNO, N (%)	70 (79.5)
FiO_2, % (median [IQR])	82 [65 - 95]
Air flow, L/min (median [IQR])	60 [50 - 60]
CPAP, N (%)	8 (9.1)
FiO_2, % (median [IQR])	67.5 [63.8 - 93.3]
Non-Rebreather or Venturi Mask, N (%)	5 (5.7)
Oxygen, L (median [IQR])	15.0 [15.0 - 15.0]
NIV, N (%)	4 (4.5)
PEEP, cmH_2O (median [IQR])	8.0 [7.3 - 9.3]
FiO_2, % (median [IQR])	72.5 [57.5 - 86.3]
SpO_2, % (median [IQR])	91.3 [89.0 - 94.0]
PaO_2, mmHg (median [IQR])	72.0 [60.0 - 84.5]

Abbreviations: CPAP: Continuous Positive Airway Pressure, HFNO: High Flow Nasal Oxygen, NIV: Non-invasive ventilation.

Epidemiology

There was no difference in the incidence of do–not–intubate orders (**Table 1**). Patients in the prone positioning group less often had a history of cardiovascular disease (**Table 1**). Other baseline characteristics were not different between the two groups. Patients in the prone positioning group had worse oxygenation, but oxygen supplementation was comparable to that in the standard care group (**Table 3**).

Table 3. Oxygen supplementation and characteristics at ICU admission day.

	Overall N = 478	**Prone Positioning N = 88**	**Standard Care* N = 390**	***P-value***
Oxygen support **				
Not known	3 (0.6)	0 (0.0)	3 (0.8)	
Nasal sprong, N (%)	24 (5.0)	1 (1.1)	23 (5.9)	
Oxygen, L (median [IQR])	4 [3 - 5]	5 [5 - 5]	4 [3 - 5]	0.376
Non-Rebreather or Venturi Mask, N (%)	60 (12.6)	9 (10.2)	51 (13.1)	
Oxygen, L (median [IQR])	15 [12 - 15]	15 [15 - 15]	15 [12 - 15]	0.038
High Flow Nasal Oxygen (HFNO), N (%)	372 (77.8)	73 (83.0)	299 (76.7)	
FiO_2, % (median [IQR])	80 [60 - 90]	80 [60 - 94]	75 [60 - 90]	0.161
Flow, Liters oxygen/min (median [IQR])	50 [50 - 60]	50 [50 - 60]	50 [50 - 60]	0.057
Non-invasive ventilation (NIV), N (%)	13 (2.7)	2 (2.3)	11 (2.8)	
PEEP, cmH_2O (median [IQR])	6 [5 - 8]	9 [7 - 11]	6 [5 - 8]	0.688
FiO_2, % (median [IQR])	50 [40 - 60]	55 [52.5 - 57.5]	50 [40 - 65]	0.481
Missing data, N (%)	6 (0.01)	3 (3.4)	3 (0.7)	
Respiratory values* **				
SpO_2, % (median [IQR])	93 [90 - 95]	91 [89 - 94]	93 [90 - 96]	<0.001
PaO_2, mmHg (median [IQR])	76 [25 - 87]	73 [61 - 83]	77 [19 - 88]	0.022

* Intubated patients at day 0 excluded
** At 6 AM on the first day after ICU admission
*** Regardless of the type of oxygen support

Treatment failure

81 (92.0%) patients in the prone positioning group versus 289 (63.1%) patients in the standard care group experienced treatment failure, the primary endpoint of this analysis (**Figure 2**). The difference in treatment failure was driven by a difference in the intubation rate before day 28, and not by a difference in mortality.

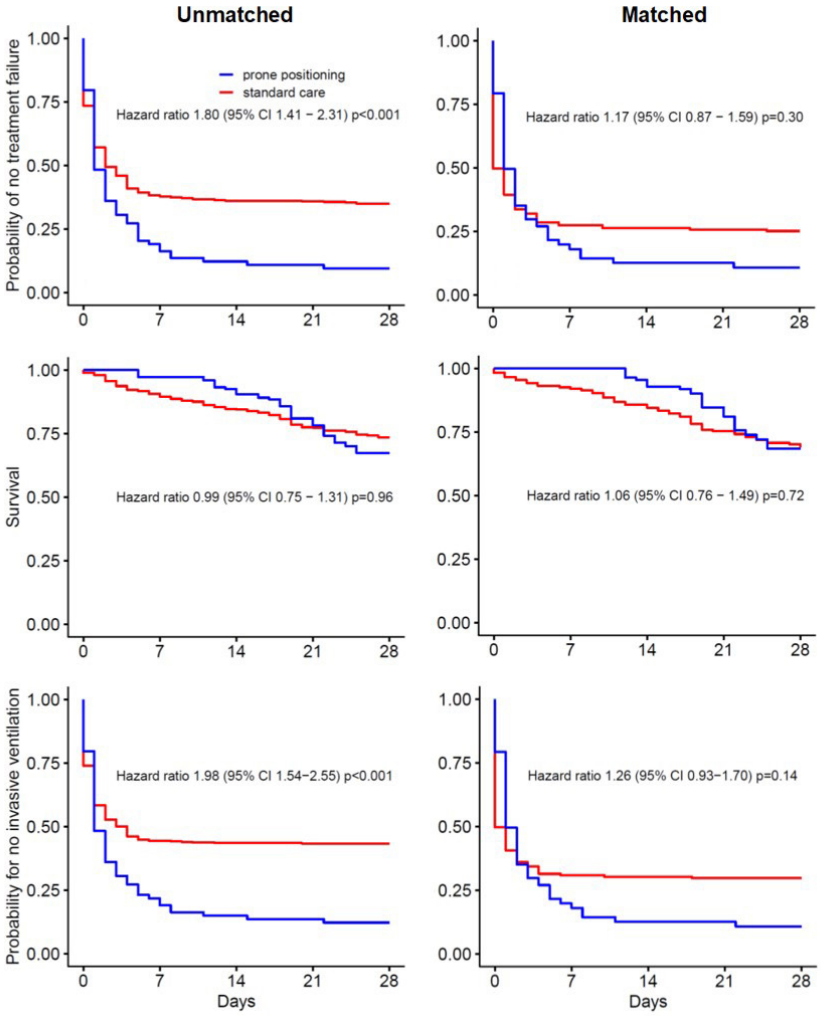

Figure 2. Patient outcomes in the unmatched (left panel) and the matched analysis (right panel).

Other outcomes
ICU and hospital length of stay were significantly longer in the prone group than in the standard care group (**supplemental file - Figure S1 A-B**); ICU and hospital mortality were not different between the groups (**supplemental file - Figure S2 A-B**).

Propensity matched analysis
We matched 70 patients in the prone positioning group to 175 patients in the standard care group (**supplemental file - Table S1**). Of 88 patients that received awake prone position, 18 patients could not be matched due to the strict margin of maximum caliper of the propensity score. Differences in treatment failure, mortality, and intubation rate before day 28 remained but were not statistically significant (**Figure 2, supplemental file - Figure S1 C-D, supplemental file - Figure S2 C-D**).

DISCUSSION

The findings of this preplanned descriptive analysis of the national multicenter observational cohort PRoAcT–COVID can be summarized as follows: (1) awake prone positioning was used in one in six patients with refractory hypoxemia due to COVID–19; (2) prone positioning started early after ICU admission, and sessions lasted for many hours but it was often stopped early because of need for intubation; (3) the only patient characteristic that had an association with prone positioning was a history of cardiovascular disease, which was more often present in standard care patients; and (4) in unmatched analysis, but not in matched analysis prone positioning had an association with treatment failure, an association that was mainly driven by a higher intubation rate.

Our study has several strengths. PRoAcT–COVID included a large proportion of all severely ill acute hypoxemic COVID–19 patients that were admitted to ICUs during the second wave of the pandemic in the Netherlands. We focused on patients that were admitted to the ICU but did not start immediately with invasive ventilation at ICU admission—in other words, patients that were severely ill and could have received the intervention of interest. We included various types of hospitals, including academic, teaching and non–teaching hospitals, contributing to the generalizability of the findings. Follow–up was complete, and there were no missing data for the primary analysis. Finally, we strictly adhered to the preplanned statistical analysis plan, and used sophisticated analyses including propensity matching to reduce the risk of confounders.

The findings of our study expand our knowledge on the practice of prone positioning in non–intubated acute hypoxemic COVID–19 patients. One RCT in intubated patients with a low P/F ratio showed that use of prone positioning

sessions for at least 16 hours to be effective.[2] Recently a systematic review reported that treatment of patients with COVID-19 was not so different compared to patients with classic ARDS.[17] Also, one recent meta-analysis showed that early use of prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19 could be beneficial.[18] However, use of awake prone positioning and its continuation seems quite variable, and details are not always clearly reported.[18] The incidence of prone positioning in our cohort was lower compared to that in one other study,[6] but similar to that in another study.[19] Duration of sessions were comparable to that in three studies.[5, 19, 20] but longer than that in another report.[12] Of interest, sessions lasted much longer than those in studies performed in general wards.[18]

Our study shows that prone positioning was used for one day in the majority of patients. This is relatively short compared to other studies, reporting that prone positioning was used for two days or longer.[18] This could affect, at least in part, the outcomes in our cohort. Differences with regard to duration of use of prone positioning between studies could be explained by differences in settings—we here studied patients that were admitted to the ICU, patients that were probably much sicker but whose care was provided by more experienced healthcare providers than in the general ward.[18] Another explanation could be that in the Netherlands, the use of awake prone positioning was relatively new at the moment of data collection and an expert consensus statement about management strategies advising awake prone positioning, was published afterwards.[9]

Our findings are supported by the results of a multicenter retrospective cohort study in 501 patients with COVID–19 and hypoxemia.[21] In that study, prone positioning offered no clinical benefit in patients who had not received mechanical ventilation. In addition, the odds of having a worse outcome at day 5 based on a modified World Health Organization ordinal scale was higher among patients receiving the awake prone positioning intervention, suggesting potential harm of this intervention in patients with acute hypoxemia due to COVID–19. Taken together, routine recommendation for awake prone positioning may not be beneficial in these patients.

The high proportion of patients receiving HFNO during awake prone positioning, is comparable to that reported in other reports.[5, 6, 22] Other oxygen interfaces were seldom, or not, used in our cohort. It could be that CPAP, non–invasive ventilation and ventilatory support with the helmet is relatively underused in the Netherlands, at least in part explaining the low incidences of these forms of oxygen support in this cohort.

The one-single difference in baseline characteristics between patients that received awake prone positioning and patients that did not receive this intervention, was a history of cardiovascular disease. Although it has been reported before that prone positioning could improve cardiac function,[3] placing a patient in a prone

position could also lead to hemodynamic instability, e.g., because of increased need for sedation – this may have led to less enthusiasm to use prone positioning in those patients.[2] This, however, remains speculative as we were not able to collect data on sedation practice.

Treatment failure occurred more often in the awake prone positioning group than in the standard care group. This finding may seem in contrast with findings of the abovementioned meta–trial of awake prone positioning.[7] Indeed, in that meta–trial treatment failure occurred less often in patients that received awake prone positioning compared to patients that received standard care. It should be realized, though, that studies in this meta–trial compared awake prone positioning with standard care in COVID–19 patients within the hospital, i.e., in patients in a general ward or in an ICU.[7] Substantial heterogeneity was also shown in a recent meta-analysis of observational studies, reporting that use of awake prone positioning was associated with a reduced mortality but not with a lower intubation rate.[20] Awake prone positioning may translate in a better outcome more if it is applied early, i.e., as a preventive measure in a general ward in patients receiving high flow oxygen support, and less if it is applied late, as a rescue treatment in an ICU. Of note, a comparable difference in treatment effects in relation to the moment of initiation was recently shown regarding therapeutic anticoagulation with heparin in COVID 19 patients.[23, 24]

The association of awake prone positioning in the unmatched-cohort with treatment failure was driven by a difference in need for intubation. One could hypothesize that the association with treatment failure results from a causal relation. Awake prone positioning could increase sputum evacuation, possibly creating an acute need for intubation in case massive amounts of sputum enter the larger airways. It should be noticed, though, that in matched analysis there were no associations of prone positioning with treatment failure.

Awake prone positioning may have the potential to improve outcomes of patients with acute hypoxemic respiratory failure due to another cause. On the other hand, awake prone positioning is an intensive and time–consuming intervention that may require training of healthcare professionals for save application. Therefore, randomized evidence is needed. One recently started multicenter randomized clinical trial investigates the effect of awake prone positioning on intubation rate and mortality in ICU patients with acute hypoxemic respiratory failure not necessarily caused by COVID–19.[25]

While a multivariate analysis may have been preferred to identify patient characteristics that are independently associated with the use of awake prone positioning, data on specific factors like respiratory rate and work of breathing could not be collected, and the sample size would be too small to draw any meaningful conclusions.

PRoAcT–COVID has limitations. As this was an observational study, variety in

practice of care and reporting could have caused inaccuracies in the data. Despite the presence of a new national guideline for use of awake prone positioning, the decision to apply awake prone positioning could still have been based on clinical expertise and reasoning by the ICU team. In line with the study design of the ProAcT-COVID study we could not collect data on practice of awake prone positioning before admission to the ICU, complications related to awake prone positioning, and changes in oxygenation or oxygen supply during awake prone positioning. While there has been evidence for involvement of the cardiovascular system in COVID-19 and COVID-19 related outcomes, unfortunately we did not collect data regarding cardiovascular complications. Selection of ICUs for this study, which was based on previous collaborations in studies of ventilation in critically ill patients, including those with COVID–19 patients,[26] may have resulted in an over–representation of ICUs with more knowledge and experience in awake prone positioning. In addition, the exclusion criteria used for this preplanned descriptive analysis may have resulted in selection bias. Finally, due to the observational nature of our data, no causal relationship can be established and the findings of the descriptive analysis in this study should be regarded as exploratory.

CONCLUSIONS

In this national multicenter observational cohort, awake prone positioning was used in one in six critically ill acute hypoxemic COVID–19 patients. In the unmatched analysis patients that received prone positioning had higher risk for treatment failure. But this was not confirmed in the matched analysis. We are in urgent need for randomized clinical trials of prone positioning in non–intubated patients with acute hypoxemia.

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SUPPLEMENTAL FILE

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Table S1. Baseline characteristics of the matched cohort

	Overall N = 245	Prone Positioning N = 70	Standard Care N = 175	*P*
Age, years (median [IQR])	66 [59 - 73]	66 [60 - 74]	66 [59 - 73]	0.726
Male gender, N (%)	172 (70.2)	45 (64.3)	127 (72.6)	0.260
BMI, kg/m2 (median [IQR])	28.4 [25.4 - 32.3]	29.3 [26.0 - 32.2]	27.8 [25.3 -32.4]	0.348
SAPS II score (median [IQR])	44 [33 - 54]	46 [36 - 54]	44 [32 - 54]	0.558
Do-not-intubate order, N (%)	6 (2.4)	0 (0.0)	6 (3.4)	0.267
Comorbidities				0.463
Arterial hypertension, N (%)	97 (39.6)	30 (42.9)	67 (38.3)	0.606
Cardiovascular disease, N (%)	60 (24.5)	10 (14.3)	50 (28.6)	0.029
Heart failure, N (%)	11 (4.5)	2 (2.9)	9 (5.1)	0.661
COPD or astma, N (%)	43 (17.6)	12 (17.1)	31 (17.7)	1.000
Diabetes mellitus, N (%)	70 (28.6)	16 (22.9)	54 (30.9)	0.273
Chronic kidney disease, N (%)	21 (8.6)	5 (7.1)	16 (9.1)	0.801
Malignancy, N (%)	14 (5.7)	3 (4.3)	11 (6.3)	0.761
Neuromuscular disease, N (%)	7 (2.9)	2 (2.9)	5 (2.9)	1.000
Obstructive sleep apnea, N (%)	16 (6.5)	4 (5.7)	12 (6.9)	0.967

Abbreviations: BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score.

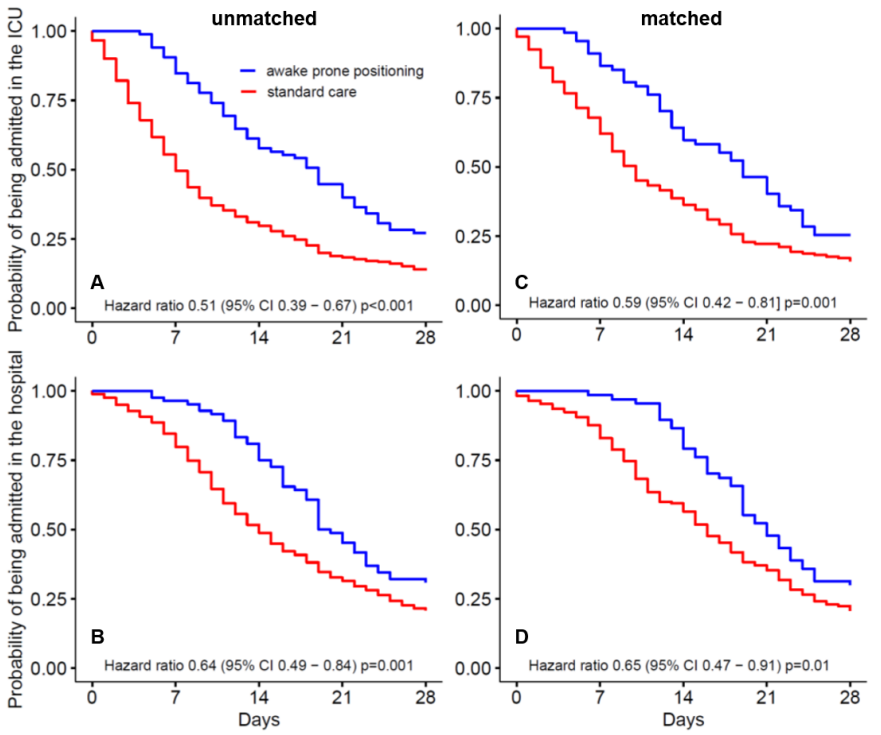

Figure S1 A-D. Unmatched and matched analysis Kaplan Meier curve for ICU and hospital LOS
A: ICU discharge unmatched, B: Hospital discharge unmatched, C: ICU discharge matched, D: Hospital discharge matched

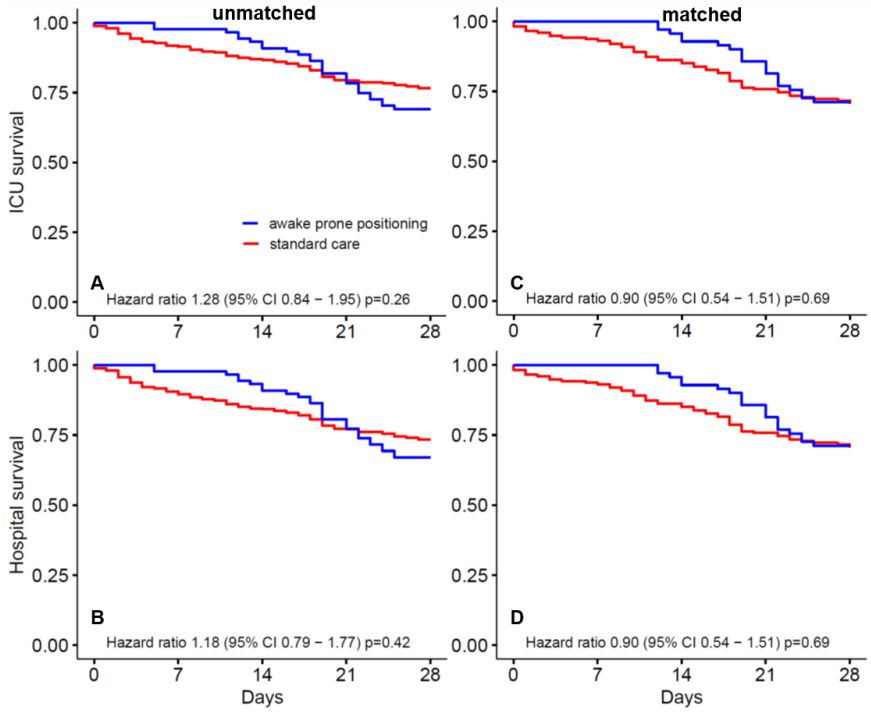

Figure S2 A-D. Unmatched and matched analysis Kaplan Meier curve for ICU and hospital mortality A: ICU mortality unmatched, B: Hospital mortality unmatched, C: ICU mortality Matched, D: Hospital mortality Matched

11 Summary

SUMMARY

Airway care interventions and prone positioning in critically ill patients

This thesis contains a series of investigations that focus on airway care interventions in invasively ventilated patients and the use of prone positioning in COVID-19 patients admitted to the intensive care.

The three overarching aims of this thesis were:
1. to determine the current practice of airway care interventions in Dutch ICUs;
2. to evaluate the available evidence for benefit of MI–E in invasively ventilated patients; and
3. to study the practice of prone positioning and its association with outcomes in critically ill COVID–19 patients.

The three overarching hypotheses tested were:
1. that current practice of airway care interventions in intubated critically ill patients is highly variable in the Netherlands;
2. that evidence for benefit of MI-E in invasively ventilated patients is scarce; and
3. that prone positioning improves outcome in critically ill COVID–19 patients.

MAIN FINDINGS

Airway care interventions in invasively ventilated patients

Chapter 2 discussed the routine use of airway interventions in invasively ventilated patients. We hypothesize that these techniques have great potential in individual cases, but we strongly argue against routine use as long as studies fail to provide robust evidence for efficacy, but certainly also for safety: 'primum non nocere'.

Chapter 3 reported the findings of a single center observational study named 'Airway Mucus in Invasively Ventilated Critically Ill Patients—an observational pilot study comparing rheology to a clinical classification system' (MICA). We tested the hypothesis that airway mucus viscoelastic properties, as measured by rheology in critically ill patients receiving invasive mechanical ventilation correlates with its clinical mucus classification score. In 41 patients, 52 mucus samples were collected. Most samples (85%) were classified as moderately viscous by healthcare professionals, while only two (4%) samples were classified as 'watery', and three samples (6%) were classified as tenacious. There was no correlation between the clinical mucus classification and the viscoelastic sputum properties, with G*: τb = -0.00072, p = 0,95. Our results showed that the clinical assessment of airway mucus

by a clinical classification scale did not correlate with its biophysical properties as measured via rheology.

In **Chapter 4** contained the results of a self–administered web-based survey sent to a single pre–appointed representative of all ICUs in the Netherlands. Our hypothesis was that current practice of, and perceptions towards airway care interventions would be highly variable due to the lack of evidence. Response rate was 85% (72 ICUs). We found substantial heterogeneity in the intensity and combinations of airway care interventions used. Most (81%) ICUs reported using heated humidification as a routine prophylactic intervention. All (100%) responding ICUs used nebulized mucolytics and/or bronchodilators; however, only 43% ICUs reported nebulization as a routine prophylactic intervention. Most (81%) ICUs used manual hyperinflation, although only initiated with a clinical indication like difficult oxygenation. Few (22%) ICUs used MI-E for invasively ventilated patients. Use was always based on the indication of insufficient cough strength or as a continuation of home use. In the Netherlands, use of routine prophylactic airway care interventions is common despite evidence of no benefit. There is an urgent need for evidence of the benefit of these interventions to inform evidence-based guidelines.

Chapter 5 and **chapter 6** reported on the protocol and results of a scoping review on MI-E in invasively ventilated patients. Based on a systematic literature search, 28 citations were taken forward for data extraction. We found that main indications reported for MI-E use during invasive ventilation were presence of secretions and mucus plugging (13/28, 46%). Perceived contraindications mostly related to use of high levels of positive pressure (18/28, 68%). Protocolized MI-E settings with a pressure of ±40 cm H_2O were most commonly used, with detail on timing, flow, and frequency of prescription infrequently reported. Various outcomes were re-intubation rate, wet sputum weight, and pulmonary mechanics. Only 3 studies reported the occurrence of adverse events. From qualitative data, the main barrier to MI-E use in invasively ventilated patients was lack of knowledge and skills. We concluded that there is little consistency in how MI-E is used and reported, and therefore, recommendations about best practices are not possible.

Chapter 7 reported on the focus group study on MI-E in invasively ventilated patients in which 35 health care professionals participated with experience in MI-E from infrequent to several years of frequent MI-E use in different patient populations. We identified four main themes: (1) knowledge; (2) beliefs; (3) clinical decision making; and (4) future adoption. Key findings were: (1) Participants agreed there is limited evidence with knowledge mainly derived from protocols from home ventilation centres. (2) MI-E was perceived as a safe and valuable element of airway

clearance and weaning protocols in the ICU, although some safety concerns were expressed regarding required pressures. (3) MI-E was initiated and influenced by available expertise and experiences. (4) More evidence and expertise with regard to MI-E in invasively ventilated critically ill patients is needed. We concluded that interprofessional knowledge and expertise of MI-E in invasively ventilated patients is limited due to minimal available evidence and adoption. Participants believed MI-E a potentially useful intervention for airway clearance and inclusion in weaning protocols when more evidence is available.

Prone positioning

Chapter 8 contained the results of a secondary analysis in the PRoVENT-COVID study on the practice of early prone positioning and the associations with outcomes. The hypothesis tested was that prone positioning improves outcome of invasively ventilated COVID-19 patients. In 734 patients, prone positioning was indicated in 60%—the incidence of prone positioning was higher in patients with an indication than in patients without an indication for prone positioning (77 vs. 48%, p = 0.001). Patients were left in the prone position for median (IQR) 15.0 (10.5 – 21.0) hours per full calendar day—the duration was longer in patients with an indication than in patients without an indication for prone positioning (16.0 (11.0 – 23.0) vs. 14.0 (10.0 – 19.0) hours, p < 0.001). Ventilator settings and ventilation parameters were not different between groups, except for FiO_2 which was higher in patients having an indication for and actually receiving prone positioning. Our data showed no difference in mortality at day 28 between the 4 groups (HR no indication, no prone vs. no indication, prone vs. indication, no prone vs. indication, prone: 1.05 (0.76 – 1.45) vs. 0.88 (0.62 – 1.26) vs. 1.15 (0.80 – 1.54) vs. 0.96 (0.73 – 1.26) (p = 0.08)). Factors associated with the use of prone positioning were ARDS severity and FiO_2. The findings of this study are that prone positioning is often used in COVID-19 patients, even in patients that have no indication for this intervention. Sessions of prone positioning lasted long. Use of prone positioning may affect outcomes.

Chapter 9 reported the results of a practical guidance for awake prone positioning in patients with COVID-19. The aim was to summarize evidence for benefit and to develop a set of pragmatic recommendations for use of awake prone positioning in patients with COVID-19 pneumonia, focusing on settings where resources are limited. A growing number of observational studies describe the effects of awake prone positioning in patients with COVID-19 pneumonia in whom hypoxemia is refractory to simple measures of supplementary oxygen. Awake prone positioning improves oxygenation in most patients, usually within minutes, and reduces dyspnea and work of breathing. The effects are maintained for up to 1 hour after turning back to supine, and mostly disappear after 6–12 hours. In available studies, awake prone positioning was not associated with a reduction in the rate of intubation

for invasive ventilation. Awake prone positioning comes with little complications if properly implemented and monitored. Pragmatic recommendations including indications and contraindications were formulated and adjusted for resource-limited settings.

Finally, **chapter 10** reported the results of a secondary analysis in the PRoAcT-COVID study on the practice of awake prone positioning and associations with outcome. The hypothesis was that prone positioning was used often, and that its use had associations with outcome. We found that in 546 ICU patients, awake prone positioning was used in 88 (16.1%) patients. Awake prone positioning started within median 1 (0 to 2) days after ICU admission, sessions summed up to median 12.0 (8.4 – 14.5) hours for median 1.0 day. In the unmatched analysis (HR, 1.80 (1.41 – 2.31); $p < 0.001$), but not in the matched analysis (HR, 1.17 (0.87 – 1.59); $p = 0.30$), treatment failure occurred more often in patients that received awake prone positioning. The findings of this study are that awake prone positioning was used in one in six COVID-19 patients. Awake prone positioning started early, and sessions lasted long but were often discontinued because of need for intubation.

12 General discussion and future perspectives

Willemke Stilma

This thesis bundles a collection of studies of (1) airway care interventions in ventilated critically ill patients in general, and (2) prone positioning in intensive care unit (ICU) patients with acute hypoxemic respiratory failure due to coronavirus disease 2019 (COVID–19). This chapter places the findings of these studies in a broader context, discusses potential implications for current practice, and provides suggestions for future research.

Airway care interventions

Invasively ventilated critically ill patients frequently undergo airway care interventions, like 'endotracheal suctioning', 'manual hyperinflation' and 'nebulizations' (**Figure 1**). Endotracheal suctioning is the most commonly used airway care intervention. Its purpose is to remove secretions from the artificial (the endotracheal tube or tracheostomy) and native airways (the trachea). Manual hyperinflation is an often–used technique that consists of a slow and deep inhalation followed by a rapid exhalation, in the hope that this mobilizes airway secretions from the smaller to the larger airways. There it can be removed easily by endotracheal suctioning. In fact, manual hyperinflation could be seen as an 'artificial cough', wherein a forceful exhalation may move mucus to the larger airways. Nebulization of mucoactive agents, by far the most frequently used airway care intervention, may facilitate mucus clearance from the airways by the other two interventions.

Figure 1. Three airway care interventions in critically ill patients

All airway care interventions have in common that they are meant to prevent mucus accumulation in the airways, thereby possibly preventing airway obstructions that may lead to collapse of lung tissue, and maybe even airway colonization that often precedes life–threatening pulmonary infections. Evidence for benefit from airway care interventions in invasively ventilated critically ill patients, however, is surprisingly absent. In addition, there is a wide variety in how these interventions are applied in daily practice. Decisions regarding their use may be more driven by beliefs then by the findings of the scarcely performed clinical studies.

Airway care interventions are often performed routinely without a clinical indication, i.e., as a standard order. If used on clinical indication, there is a wide variation in what triggers the use of an airway care intervention. It could be that the caregivers do not have proper 'tools', i.e., measures to base the decision

on when to apply a certain airway care intervention. Mucus composition and characteristics are often suggested to be used in the decision to perform an airway care intervention, but classification of mucus is easier said than done: it often uses very subjective criteria, like 'watery', 'viscous' or 'tenacious', and we showed that these subjective measures by far do not align with objective rheology measures. Future research should focus and deliver a practical but foremost reliable mucus classification. This then can be used in future randomized clinical trials that test the efficacy of airway care interventions in invasively ventilated patients.

Another point of concern is that airway care interventions are not without risks for the critically ill patient. For instance, these interventions often require a disconnection from the ventilator during which airway pressures are lost—this could potentially cause hypoxemia due to collapse of lung tissue. Often, they also cause short periods of no or too little ventilation—this could lead to hypercapnia. Next, higher than normal volumes and pressures could impact cardiac performance—this could compromise the circulation. Last but not least, endotracheal suctioning could damage the upper airways—this could lead to life–threatening bleedings, in particular in patients with coagulation disorders or those receiving anticoagulants. Therefore, future randomized clinical trials should not only focus on the efficacy of airway care interventions, but also their safety.

A third concern is that most airway care procedures are perceived by patients as painful and stressful. For instance, both endotracheal suctioning and manual hyperinflation are often remembered by patients as one of the most stressful and painful procedures during care in the ICU. Another airway care intervention, nebulization of acetylcysteine, is frequently recollected as a stressful event because of the bad odor that comes with the use of this agent. Future studies need to focus on these aspects as well.

A last and growing concern are the costs associated with care for ventilated critically ill patients, which included the costs associated with airway care interventions: 'direct' costs, related to the disposables used with each intervention; 'indirect' costs, associated with the time used by healthcare workers in performing a certain intervention; and 'environmental' costs, caused by the medical waste that is produced with all these interventions. The last two factors are discussed in more detail below.

It should be stressed that 'if it does not help, it does not hurt' does not apply to airway care interventions. If future studies show a certain airway care intervention to have only little or even lacks benefit, and instead proofs to be potentially harmful or costly, we may need to decide to no longer perform that intervention in ventilated critically ill patients.

Mechanical insufflation–exsufflation

Mechanical insufflation–exsufflation (MI–E) devices can be used to create an 'artificial cough'. Currently, these devices are used in patients with neuromuscular disease, to prevent respiratory complications associated with mucus retention. A MI–E device delivers a deep inhalation by applying a certain level of positive pressure, followed by a forceful exhalation by applying a certain level of negative pressure, as if a patient is coughing (**Figure 2**).

Figure 2. Mechanical insufflation-exsufflation device

There is growing interest in the use of MI–E devices in ventilated critically ill patients. MI–E could be an effective, safe, and maybe less–traumatizing airway care intervention then those discussed in the previous chapter. Its use may even reduce the need for the other airway care interventions. However, robust evidence for benefit of MI–E in ventilated critically ill patients remains lacking, and is urgently needed.

First, we need to understand better how feasible and safe MI–E is in ventilated critically ill patients. Therefore, we designed a study, named 'a mechanical insufflation–exsufflation (cough assist) in critically ill adults' (ACACIA) (clinicaltrials.gov; under review). The primary aim of this study is to evaluate the feasibility of use of MI–E devices in invasively ventilated critically ill patients. One secondary aim is to evaluate its safety. Furthermore, we also want to explore its effect on the need for other airway care interventions. Last but not least, we hope to learn more about the potential effects on typical ICU outcomes, like duration of ventilation and mortality. This pilot study will include a total of 50 invasively ventilated critically ill patients that are expected to need invasive ventilation for the next 48 hours.

Patients are randomly assigned to the 'MI–E group', in which ICU nurses will apply MI–E sessions in the morning and afternoon on top of standard airway care, or the control group, in which only standard airway care is applied. The primary outcome of ACACIA is the number of successfully delivered MI–E sessions per patient (feasibility). Secondary outcomes include serious adverse events like pneumothorax, pulmonary and hemodynamic instability (safety). ACACIA will

also provide information for the power calculation of future studies (efficacy). If ACACIA shows MI–E to be feasible and safe, we will design a sufficiently powered randomized clinical trial. This follow–up study must also explore how patients experience this intervention, and its cost–effectiveness.

Prone positioning

Prone positioning is increasingly used in invasively ventilated patients with moderate to severe acute respiratory distress syndrome (ARDS), as studies have provided convincing evidence for benefit in these patients.[1] Prone positioning can improve oxygenation in several ways (**Figure 3**). Opposite to in the supine position, in the prone position the heart is positioned in the 'back' of the thorax—this means that it can no longer cause atelectasis of the dependent lung tissue. In the prone position, the chest wall compliance and distribution of aeration improves—with that intrapulmonary shunt decreases. Another aspect of prone positioning is that the diaphragm is no longer pushed upward by the weight and volume of the abdomen as in a supine position—as such, prone positioning can recruit lung tissue, and this could improve the outcome of ventilation. Last but not least, in the prone position the direction of the trachea changes from 'downwards' to 'upwards'—as such, prone positioning may facilitate mucus mobilization and its evacuation.

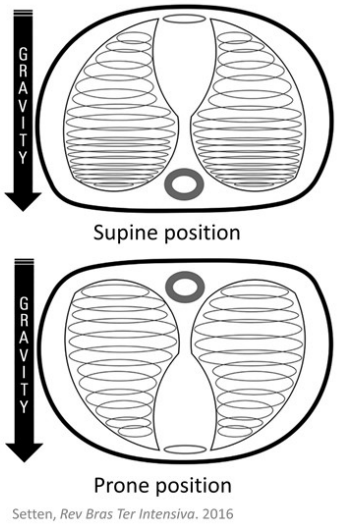

Figure 3. Impression of intra-thoracic change during prone position

Prone positioning, however, also comes with negative aspects. In patients that are in the prone position, there is a risk of tube obstruction and patients may develop pressure ulcers. Next, prone positioning is a time–consuming and resource–intensive intervention, and the procedure requires a high alertness and a trained team of healthcare professionals to be safely performed.

Before the currently ongoing COVID–19 pandemic, prone positioning was recommended to be used only in invasively ventilated patients with moderate to severe ARDS, or more specifically in patients with PaO_2/FiO_2 < 150 mm Hg. During the pandemic, prone positioning started to become one of the most frequently used rescue therapies for hypoxemia patients with COVID–19 ARDS. It is very well possible that COVID–19 pneumonia is a form of ARDS that responds better to prone positioning than other forms of ARDS. Indeed, the findings of one randomized clinical trial suggest that personalized mechanical ventilation tailored to lung morphology, i.e. early prone positioning, may be better than a high airway pressure strategy in ARDS patients with non–recruitable lung lesions,[2] which may be typical to COVID–19 ARDS.

There is increasing interest in prone positioning in patients that are not intubated, an intervention that is often called 'awake prone positioning' or 'self–proning'. These terms are slightly confusing, since neither the term 'awake' is not a synonym for 'non-intubated' nor is it that non–intubated do not need help with turning from the supine to the prone position. Already before the pandemic there were plans to study the effect of this intervention on diverse clinically relevant endpoints.[3] Early in the COVID–19 pandemic, when the intervention became popular in acute hypoxemic patients due to this infection, one meta–trial in COVID–19 patients showed awake prone positioning to reduce 'treatment failure', a composite endpoint consisting of need for intubation and mortality.[4]

Future studies of awake prone positioning are urgently needed to confirm these findings, in COVID–19 patients but also in patients with acute hypoxemic respiratory failure due to another cause. These studies should focus on its feasibility, safety, and of course also its efficacy. It could be interesting to evaluate the effects of (awake) prone positioning on mucus mobilization as this may help identifying patients that may benefit even more from this intervention, e.g., patients with a high risk of mucus accumulation.

ICU workloads

Care for critically ill patients is costly, time–consuming and resource–intensive. In the ICU, the organ functions are being supported or taken over by devices, and several healthcare professionals work together as a team in several shifts per day.[5] Typically, one ICU nurse is taking care of one or two patients, depending on how sick patients are, and the type and number of interventions needed.

In the early phases of the current COVID–19 pandemic, the workload of ICU

nurses increased dramatically. First, the numbers of patients increased rapidly—the ICU community had never seen so many critically ill patients that needed full respiratory support in such a short period of time. Second, most patients were to be treated in isolation, which also increases the workloads. This increase in workload had a clear impact on the wellbeing of ICU nurses, and resulted in an increased intention–to–leave the profession.[6] This came on top of predictions years before the pandemic regarding the available healthcare professionals in relation to the rising numbers of patients in need of critical care.[7] Thus far, there has been no signal that this prediction was wrong.

In addition, we are facing huge restrictions of capacity limited by financial budget.[8] Even though many students are being trained to become a professional nurse every year, it is impossible to keep up with the needs. Many nurses leave the profession for several reasons, like the heavy workloads and increased complexity of care. Although nurses would like to follow additional training to improve competences, education budgets for nurses are low, and following additional trainings is frequently impossible, due to the pressure on working schedules.[9] As a consequence, or at least in part due to these factors, 40% of the students that finish their training leave the profession already within two years.

Related to this we need to choose better what interventions we should or should not perform in the restricted time we have for an individual patient. An ICU nurse can easily spend more than one hour per 24 hours per patient for airway care interventions. Time spend on prone positioning easily becomes more than that. Until now, it was uncommon to study the effect of specific interventions on ICU nursing workloads. Seen the upcoming restrictions, this will be inevitable.

ICU sustainability

Another worrying aspect of ICU care is the amount of waste that is produced with the care for critically ill patients. In the Netherlands, healthcare is responsible for 7% of the nationwide CO_2 emission.[9] It is not surprising that most waste is being produced in the ICU setting. For example, care for ~2.500 critically ill patients in one ICU in one year comes with some 250.000 kg of waste. Per day, care for one singly ICU patient comes with 17 kg of mass and 12 kg of CO_2, and uses up 300 liter of water.[10] The disposables used in the ICU contribute most to the produced waste.

Currently, the high use of disposables is defended by the suggestion that this prevents infections and therefore the outcome. While we cannot deny that this may work, to a certain level, we can also not close our eyes to what we need to use for the assumed benefit. For example, the decision to eliminate running water from the tabs in the ICU in the Amsterdam UMC, to prevent infections with bacteria that grow in the tab system resulted in an increased use of hand gloves, disinfection liquids, and plastic bottles with water. For an average ICU patient, approximately 3 plastic bottles of water are used, per each day. The infection rates may have come

down, albeit that this was never formally tested, but the 'medical' waste increased largely, if not in an unacceptable way.

Care in an ICU comes with an important CO_2–footprint. Our profession needs to place all interventions, including airway care interventions against this background. Future research will need to study this aspect as well.

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13 Nederlandse samenvatting

SAMENVATTING

Luchtwegzorg interventies en buikligging bij intensive care patiënten

Dit proefschrift bevat een serie onderzoeken die gericht zijn op luchtwegzorg interventies en het gebruik van buikligging bij patiënten met COVID-19 op een intensive care.

De overkoepelende doelstellingen waren:
1. te bepalen wat de huidige praktijk is van luchtwegzorg interventies in Nederlandse intensive care afdelingen;
2. het beschikbare wetenschappelijk bewijs te evalueren voor het gebruik van de hoestmachine bij invasief beademde patiënten; en
3. te onderzoeken wat de praktijk is van buikligging en de associaties met uitkomsten bij intensive care patiënten met COVID-19.

De getoetste hypothesen zijn:
1. dat de huidige praktijk van luchtwegzorg interventies in invasief beademde patiënten zeer gevarieerd is in Nederland;
2. dat het bewijs voor voordeel van het gebruik van de hoestmachine bij invasief beademde patiënten schaars is; en
3. dat buikligging de uitkomsten verbetert van intensive care patiënten met COVID-19.

Luchtwegzorg interventies bij invasief beademde patiënten

Hoofdstuk 2 bevatte een discussie waarin we onderschrijven dat luchtwegzorginterventies in individuele gevallen de potentie hebben om uitkomsten te verbeteren, maar dat voorzichtigheid geboden is om deze interventies routinematig preventief toe te passen bij alle patiënten, zolang studies geen bewijs hebben kunnen leveren dat dit effectief en veilig is: 'primum non nocere' (ten eerste, doe geen kwaad).

Hoofdstuk 3 rapporteerde de resultaten van een observationele studie waarin de sputum classificatie door verpleegkundigen werd vergeleken met een reologie metingen. We konden geen verband vinden tussen de sputum classificatie en de reologie waarden.

In **hoofdstuk 4** rapporteerden we de resultaten van een vragenlijstonderzoek naar de huidige praktijk van luchtwegzorg op Nederlandse IC-afdelingen. De hypothese was dat de huidige praktijk en overtuigingen in relatie tot luchtwegzorg zeer gevarieerd was. 85% (72 IC-afdelingen) heeft meegedaan. Wij hebben

een grote variatie gezien in de intensiteit en de combinaties van luchtwegzorg handelingen die werden gebruikt. De meeste (81%) IC-afdelingen gebruikten actieve bevochtiging als routinematige preventieve interventie. Alle IC-afdelingen (100%) gebruikten verneveling van medicatie, hoewel slechts 43% van de IC-afdelingen aangaf dit routinematig toe te passen bij iedere patiënt. De meeste (81%) IC-afdelingen gebruikten balloneren als daar een klinische indicatie zoals moeilijke oxygenatie voor was. Enkele (21%) IC-afdelingen gebruikten de hoestmachine bij invasief beademde patiënten. Dit gebruik was altijd gebaseerd op een ineffectieve hoest of om het gebruik vanuit huis te continueren. Het preventief en routinematig gebruik van luchtwegzorg handeling is gebruikelijk in Nederland, ondanks dat het wetenschappelijk bewijs hiervoor ontbreekt. Het is belangrijk dat hier meer onderzoek naar wordt gedaan zodat richtlijnen kunnen worden ontwikkeld.

Hoofdstuk 5 en **hoofdstuk 6** bevatten het protocol en de resultaten van een literatuuronderzoek naar het gebruik van de hoestmachine bij invasief beademde patiënten. De resultaten uit 28 artikelen zijn gerapporteerd. De belangrijkste reden om de hoestmachine te gebruiken was de aanwezigheid van slijm en mucus pluggen (13/28, 46%). De belangrijkste reden om de hoestmachine niet te gebruiken was het gebruik van hoge beademingsdrukken (18/28, 68%). Geprotocolleerd gebruik van de hoestmachine was meestal met drukken van ±40 cm H_2O, waarbij details over stroomsnelheden en frequenties onregelmatig gerapporteerd waren. Verschillende uitkomstmaten waren her-intubaties, sputum gewicht en longfuncties. Slechts drie studies rapporteerden over het optreden van complicaties. Het ontbreken van kennis en expertise waren een belangrijke barrière voor gebruik van de hoestmachine. Concluderend is er weinig consistentie in de manier waarop de hoestmachine wordt gebruikt en gerapporteerd, een advies over de beste wijze van gebruik is dan ook niet mogelijk.

Hoofdstuk 7 beschreef de resultaten van een focusgroep studie over het gebruik van de hoestmachine bij invasief beademde patiënten met 35 zorgprofessionals die ervaring hadden met de hoestmachine bij intensive care patiënten. Vier thema's kwamen hieruit naar voren: (1) kennis; (2) overtuigingen; (3) klinische besluitvorming en (4) toekomstmogelijkheden. De belangrijkste bevindingen waren:

(1) Deelnemers waren het eens dat er beperkt bewijs beschikbaar is voor het gebruik en dat de meeste kennis voortkwam uit het centrum voor thuisbeademing.
(2) De hoestmachine werd gezien als een veilig en waardevol onderdeel van luchtwegzorg en ontwenning van de beademing, alhoewel er wel zorgen waren over de veiligheid hiervan in relatie tot gegeven drukken.

(3) Het inzetten van de hoestmachine werd bepaald door de aanwezige expertise en ervaringen.
(4) Meer wetenschappelijk bewijs en expertise is nodig voor het gebruik van de hoestmachine bij invasief beademde patiënten. De conclusie was dat de kennis en expertise beperkt is als gevolg van weinig bewijs en gebruik. Deelnemers zagen wel mogelijkheden voor de hoestmachine in de toekomst als dit ondersteund zou zijn door wetenschappelijk bewijs.

Buikligging

Hoofdstuk 8 bevatte de resultaten van een secundaire analyse van de PRoVENT-COVID-studie over het gebruik van buikligging bij invasief beademde patiënten met COVID-19. De hypothese was dat buikligging de uitkomsten van invasief beademde patiënten met COVID-19 kan verbeteren. Van de 734 patiënten met een indicatie voor buikligging is dit toegepast in 60%. De incidentie was hoger dan bij patiënten zonder indicatie voor buikligging (77 vs. 48%, p = 0.001). Patiënten werden op de buik gelegd voor een periode van mediaan (IQR) 15.0 (10.5 – 21.0) uur per kalenderdag. De duur was langer bij patiënten met een indicatie dan zonder een indicatie voor buikligging (16.0 (11.0 – 23.0) vs. 14.0 (10.0 – 19.0) uur, p < 0.001). Beademingsinstellingen waren niet verschillend tussen de groepen, met uitzondering van de toegediende zuurstofconcentratie. Deze was hoger bij patiënten met een indicatie voor buikligging die ook daadwerkelijk op de buik lagen. Onze data laten zien dat er geen verschil was in overlijdensrisico op dag 28 tussen de vier groepen (HR geen indicatie, geen buikligging vs. geen indicatie, buikligging vs. indicatie, geen buikligging vs. indicatie, buikligging: 1.05 (0.76 – 1.45) vs. 0.88 (0.62 – 1.26) vs. 1.15 (0.80 – 1.54) vs. 0.96 (0.73 – 1.26) (p = 0.08)). De resultaten van deze studie laten zien dat buikligging vaak is toegepast bij patiënten met COVID-19, zelfs bij patiënten die hier geen indicatie voor hadden. Sessies van buikligging duurden lang. Er zou een verband kunnen zijn met uitkomsten.

In **hoofdstuk 9** omvatte de praktische richtlijn die met een internationale en multidisciplinaire groep van 35 zorgprofessionals uit 13 verschillende landen is opgesteld. Het doel was om praktische aanbevelingen toe doen voor het gebruik van wakkere buikligging bij patiënten met COVID-19. Een toenemend aantal observationele studies beschreven het effect van wakkere buikligging bij patiënten met COVID-19 die niet reageerden op eenvoudige zuurstof toediening. Wakkere buikligging verbetert de zuurstofopname, vaak al binnen enkele minuten en verminderd benauwdheid en de ademhalingsinspanning. Dit effect houdt aan tot 1 uur na terugdraaien op de rug en verdwijnt meestal na 6-12 uur. In de beschikbare studies was er geen relatie tussen wakkere buikligging en een voorkomen van een intubatie. Wakkere buikligging gaat gepaard met weinig complicaties indien goed geïmplementeerd en gemonitord. Pragmatische aanbevelingen, inclusief

indicaties en contra-indicaties zijn geformuleerd en aangepast voor gebruik in situaties met beperkte beschikbaarheid van middelen.

Tot slot bevatte **hoofdstuk 10** de resultaten van een secundaire analyse van de PRoAcT-COVID studie naar het gebruik van wakkere buikligging bij intensive care patiënten. De hypothese was dat wakkere buikligging vaak gebruikt zou zijn en dat er een verband was met uitkomsten. We zagen dat in de groep van 546 IC-patiënten, bij 88 (16.1%) patiënten wakkere buikligging was toegepast. Wakkere buikligging begon mediaan op dag 1 (0-2) na opname op de IC-afdeling. Sessies duurden mediaan 12 (8.4 – 14.5 uur) en meestal voor 1 dag. In de niet-gematchte analyse (HR, 1.80 (1.41 – 2.31); $p < 0.001$), maar niet in de gematchte analyse (HR, 1.17 (0.87 – 1.59); $p = 0.30$), kwam een gecombineerd eindpunt van intubatie of overlijden, vaker voor bij patiënten die wakkere buikligging hadden ervaren. De resultaten van deze studie laten zien dat wakkere buikligging is toegepast bij 1 op de 6 patiënten met COVID-19 op de IC-afdeling. Wakkere buikligging werd snel ingezet na opname op de IC-afdeling, duurde lang, maar werd vaak gestopt omdat de patiënt geïntubeerd moest worden.

Addendum

AUTHOR CONTRIBUTIONS

Chapter 2

Preventing mucus plugging in invasively ventilated intensive care unit patients—routine or personalized care and 'primum non nocere'

Manuscript preparation:	W. Stilma and F. Paulus wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	M.J. Schultz

Chapter 3

Airway mucus in invasively ventilated critically ill patients—an observational pilot study comparing rheology to a clinical classification system

Study conception and design:	W. Stilma, R.S. Linssen, R.A. Bem, L.D.J. Bos, F. Paulus, M.J. Schultz.
Acquisition of data:	W. Stilma, R.S. Linssen, T.A. Lilien, O. Elsayed, A. Saatpoor.
Data analysis:	W. Stilma, R.S. Linssen, T.A. Lilien, R.A. Bem.
Manuscript preparation:	W. Stilma, R.S. Linssen and T.A. Lilien wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	R.S. Linssen and R.A. Bem.
Funding acquisition:	W. Stilma, F. Paulus, M.J. Schultz, R.A. Bem.

Chapter 4

Airway care interventions for invasively ventilated critically ill adults – a Dutch national survey

Study conception and design:	W. Stilma, S.M. van der Hoeven, F. Paulus, L. Rose, W.J.M. Scholte op Reimer, M.J. Schultz.
Acquisition of data:	W. Stilma, S.M. van der Hoeven
Data analysis:	W. Stilma, S.M. van der Hoeven, F. Paulus.
Manuscript preparation:	W. Stilma, S.M. van der Hoeven wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	L. Rose and F. Paulus
Funding acquisition:	W. Stilma, F. Paulus, M.J. Schultz.

Chapter 5

The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults: a scoping review protocol

Study conception and design:	E.L. Swingwood, W. Stilma, L.N. Tume, F. Cramp, F. Paulus, M.J. Schultz, W.J.M. Scholte op Reimer and L. Rose.
Manuscript preparation:	W. Stilma and E.L. Swingwood wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	L. Rose
Funding acquisition:	W. Stilma, F. Paulus, M.J. Schultz.

Chapter 6

The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults: a scoping review

Study conception and design:	E.L. Swingwood, W. Stilma, L.N. Tume, F. Cramp, S. Voss, J. Bewley, G. Ntoumenopoulos, M.J. Schultz, W.J.M. Scholte Op Reimer, F. Paulus, and L. Rose.
Acquisition of data:	W. Stilma, E.L. Swingwood.
Data analysis:	W. Stilma, E.L. Swingwood.
Manuscript preparation:	W. Stilma and E.L. Swingwood wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	L. Rose
Funding acquisition:	W. Stilma, F. Paulus, M.J. Schultz.

Chapter 7

Mechanical Insufflation-Exsufflation for invasively ventilated critically ill patients – a focus group study

Study conception and design:	W. Stilma, L. Verweij, B. Spek, W.J.M. Scholte op Reimer, M.J. Schultz, F. Paulus, L. Rose
Acquisition of data:	W. Stilma and F. Paulus
Data analysis:	W. Stilma and L. Verweij.
Manuscript preparation:	W. Stilma wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	L. Rose

Funding acquisition:	W. Stilma, F. Paulus, M.J. Schultz.

Chapter 8

Incidence and practice of early prone positioning in invasively ventilated COVID–19 patients — insights from the PRoVENT–COVID observational study

Study conception and design:	W. Stilma, D.M.P. van Meenen, C.M.A. Valk, H. de Bruin, F. Paulus, A.S. Neto and M.J. Schultz.
Acquisition of data:	PRoVENT-COVID Collaborative Group.
Data analysis:	W. Stilma, D.M.P. van Meenen and A.S. Neto.
Manuscript preparation:	W. Stilma, D.M.P. van Meenen and C.M.A. Valk wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	M.J. Schultz, F. Paulus and A.S. Neto

Chapter 9

Awake proning as an adjunctive therapy for refractory hypoxemia in non-intubated patients with COVID-19 acute respiratory failure – guidance from an international group of healthcare workers

Study conception and design:	W. Stilma, F. Paulus, M.J. Schultz.
Acquisition of data:	W. Stilma, L. Pisani, L.D.J. Bos, F. Paulus. M.J. Schultz.
Data analysis:	W. Stilma, L. Pisani, L.D.J. Bos, F. Paulus. M.J. Schultz.
Manuscript preparation:	W. Stilma, L. Pisani, L.D.J. Bos and F. Paulus wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	M.J. Schultz.

Chapter 10

Practice of awake prone positioning in critically ill COVID–19 patients—insights from the PRoAcT–COVID study

Study conception and design:	W. Stilma, C.M.A. Valk, D.M.P. van Meenen, L. Morales, D. Remmelzwaal, S.N. Myatra, A. Artigas, A.S. Neto, F. Paulus, M.J. Schultz.
Acquisition of data:	PRoAcT-COVID Collaborative Group
Data analysis:	W. Stilma, C.M.A. Valk, D.M.P. van Meenen, A.S. Neto.

Manuscript preparation:	W. Stilma, C.M.A. Valk and D.M.P. van Meenen wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.
Project supervision:	F. Paulus and M.J. Schultz

LIST OF PUBLICATIONS OUTSIDE THIS THESIS

Peer reviewed

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Rijkenberg S, **Stilma W**, Bosman RJ, van der Meer NJ, van der Voort PHJ. Pain Measurement in Mechanically Ventilated Patients After Cardiac Surgery: Comparison of the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT). J Cardiothorac Vasc Anesth. 2017 Aug;31(4):1227-1234.

van Meenen DMP, van der Hoeven SM, Binnekade JM, de Borgie CAJM, Merkus MP, Bosch FH, Endeman H, Haringman JJ, van der Meer NJM, Moeniralam HS, Slabbekoorn M, Muller MCA, **Stilma W**, van Silfhout B, Neto AS, Ter Haar HFM, Van Vliet J,Wijnhoven JW, Horn J, Juffermans NP, Pelosi P, Gama de Abreu M, Schultz MJ, Paulus F. Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation: A Randomized Clinical Trial. JAMA. 2018 Mar 13;319(10):993-1001.

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van Meenen DMP, Algera AG, Schuijt MTU, Simonis FD, van der Hoeven SM, Neto AS, Abreu MG, Pelosi P, Paulus F, Schultz MJ; **NEBULAE**; PReVENT; RELAx investigators. Effect of mechanical power on mortality in invasively ventilated ICU patients without the acute respiratory distress syndrome: An analysis of three randomised clinical trials. Eur J Anaesthesiol. 2023 Jan 1;40(1):21-28.

As collaborator of the PROVENT – COVID study

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Roozeman JP, Mazzinari G, Serpa Neto A, et.al. Prognostication using SpO2/FiO2 in invasively ventilated ICU patients with ARDS due to COVID–19 – Insights from the PRoVENT–COVID study. J Crit Care. 2022 Apr;68:31-37.

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As collaborator of the PRoAcT – COVID study

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As collaborator of the Amsterdam UMC COVID-19 Biobank Investigators

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de Bruin S, Bos LD, van Roon MA, et.al. Clinical features and prognostic factors in Covid-19: A prospective cohort study. EBioMedicine. 2021 May;67:103378.

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Kullberg RFJ, de Brabander J, Boers LS, et.al. Lung Microbiota of Critically Ill Patients with COVID-19 Are Associated with Nonresolving Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2022 Oct 1;206(7):846-856.

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Other

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F. Aarts, 8 vragen over buikligging bij covid-patienten, interview **W. Stilma** en Lisa Maduro, in: Nursing, juni 2021, p. 35 – 37.

De Meetlat | Cross-sectioneel onderzoek, **W. Stilma** en S. Rijkenberg, in TvZ, 5 januari 2022.

PHD PORTFOLIO

Name PhD student:	Willemke Stilma
PhD period:	2017 – 2023
PhD supervisors:	prof dr. M.J. Schultz
	prof dr. W.J.M. Scholte op Reimer
PhD co-supervisors:	prof. dr. L. Rose
	dr. F. Paulus

1. PhD training

	Year	Workload (ECTS)
Courses		
• End Note Medical library AMC	2017	0.1
• The AMC World of Science	2019	0.6
• NFU e-Brok	2019	1.5
• Qualitative research module Master EBP AMC/ UVA	2018	6
• Computing in R	2018	0.4
• Oral presentation in English	2019	0.8
• Text analysis in R (Leuven)	2019	0.6
• Systematic Reviews	2020	0.7
• Project management	2020	0.6
• Writing a scientific article (Taalcentrum VU)	2021	2
• Weekly researchmeeting ICU - AmsterdamUMC	2017 - 2023	8
Seminars, workshops and master classes		
• Back to the Future (Gelre)	Feb 2017	0.3
• MICE (Amsterdam)	Sept 2018	0.3
• NWO Laureatendag	Jan 2020	0.2
Oral presentations (selection)		
• Workshop EfCCNa MI-E in ICU	Feb 2019	0.5
• Workshop weaning conference MI-E in ICU	Nov 2019	0.5

• ESCIM digital oral presentation: 'Awake Proning in patients with COVID-19' (online)	Dec 2020	0.5
• Webinar on Nursing practice: 'Awake Proning in patients with COVID-19' (online)	April 2021	0.5
• Webinar Journal of Nursing 'EBP en onderwijs' (online)	June 2021	0.5
• Workshop Critical Care Urban Vitality (online)	June 2021	0.5
• ERS oral presentation 'Awake Proning in patients with COVID-19' (online)	Sept 2021	0.5
• EfCCNa webinar 'Awake Proning in patients with COVID-19' (online)	Sept 2021	0.5
• EfCCNa Congress Utrecht 'A focus group study on MI-E in invasively ventilated patients'	Sept 2022	0.5
• EfCCNa Congress Utrecht 'Prone positioning in invasively ventilated patients with COVID-19'	Sept 2022	0.5
• Master Evidence Base in Health Care (lustrum) together with F. Paulus	Nov 2022	0.5

Poster presentations

• Poster presentation ERS conference Madrid	Oct 2019	0.5
• Poster presentation ERS Berlin	Feb 2020	0.5
• ESCIM lives 2022 Paris poster presentation	Oct 2022	0.5

(Inter)national conferences

• EfCCNa, Ljubljana	Feb 2019	0.75
• ERS congress - Madrid	Oct 2019	0.75
• 7th European Conference on Weaning and Rehabilitation in Critically ill Patients	Nov 2019	0.3
• ERS Respiratory Failure and Mechanical Ventilation Conference - Berlin	Feb 2020	0.75
• Nursing webinar (online)	Apr 2021	0.3
• ERS conference (online)	Sept 2021	0.75
• ESCIM conference (online)	Dec 2020	0.75
• IC-Gelre Symposium	June 2022	0.3
• EfCCNa – Utrecht	Aug 2022	0.75
• ESCIM conference (Paris)	Oct 2022	0.75

• European Nursing Conference (online)	Oct 2022	0.3
• Congres acute cluster (Utrecht)	Nov 2022	0.3

Other

• Reviewing several articles yearly (Journal Nursing Critical Care, Frontiers and Sage)	From 2021	2
• Clinical work during the first wave of the pandemic (March – May 2020 Intensive Care)	2020	4.5

International visits

• Stockholm (Karolinska institute & Danderyd hospital)	2021	0.3
• London (St Thomas' Hospital & Kings'college)	2022	0.3
• Bristol (University Hospitals Bristol and Weston & UWE Bristol)	2022	0.3

2. Lecturing

• Master in Critical Care (HvA)	2018 - present	10
• Lecturing Nursing (HvA)	2015 - present	30
• Clinical training fellows ICU in MI-E	March 2019	0.5
• Clinical training ICU nursing team airway care	Spring 2021	1.0
• Clinical training ICU nursing team MICA study	Sept 2021	1.0
• Clinical training ICU nursing team MI-E	Spring 2022	1.0
• Clinical training fellows ICU airway care	Feb 2022	0.5

3. Parameters of Esteem

Grants

• NWO grant Promotiebeurs voor leraren	2018
• Stimuleringsgelden Hogeschool van Amsterdam – Duurzame luchtwegzorg op de ICU	2023

Awards and Prizes

• Course 'Ik en de Anderen' 664 (De Baak)	2021
• Anna Reynvaan praktijkprijs	2022

Audio-visual

- Podcast buikligging COVID-19 patiënten – Willemke Stilma https://hvana.nl/luister/86/even-doorpraten-waarom-leggen-verpleegkundigen-sommige-covidpatienten-op-hun-buik 2021
- 'Achter de schermen' - regie Hannah van Tassel Documentaire onderwijs tijdens de COVID pandemie 2022

DANKWOORD

Toen ik 'ja' zei tegen een pre-promotiejaar, begon ik aan een nieuwe reis. In mijn bagage had ik enige ervaring met het doen van wetenschappelijk onderzoek en de wens om een bijdrage te leveren aan de ontwikkeling van de verpleegkundige zorg op de Intensive Care. Van de hoestmachine had ik eigenlijk nog nooit gehoord. Ik stapte op een trein met wetenschappers, zorgprofessionals en studenten. Ik begon aan een reis waarin ik heb geleerd om steeds opnieuw te kijken naar wat er staat en wat dat betekent, waarin ik nieuwe dingen mocht en moest leren, ook als dat moeilijk was. Dat ik hier nu sta, heb ik te danken aan alle mensen die ik tegenkwam op deze reis. Een paar mensen wil ik expliciet bedanken.

Marcus, de aanhoudende betrokkenheid en snelheid waarmee je reageerde op manuscripten of vragen gaven deze reis een hoge snelheid. Dit zorgde voor druk, maar je gaf me ook het vertrouwen dat ik het kon. Je gaf me de ruimte om nieuwe projecten erbij te doen, zoals de MICA studie en de Guidance, waar ik met plezier veel van heb geleerd. Je ideeën en manier van onderzoek doen zijn inspirerend en ik ben je ongelooflijk dankbaar voor de begeleiding en mogelijkheden die je me hebt gegeven.

Frederique, onze samenwerking is bijzonder. Je hebt me gestimuleerd om het pad van de wetenschap in te slaan. Je hebt me op een liefdevolle manier begeleid in mijn ontwikkeling van jonge steeds verwonderende en soms extreem eigenwijze onderzoeker, naar de wetenschapper die ik nu ben. En kijk waar we nu staan! Dank voor alle bijzondere momenten en ik kijk uit naar de toekomstige projecten die we gaan doen.

Wilma, dank voor de mogelijkheid om als docent bij de HvA te starten aan een promotietraject. Je betrokkenheid bij wetenschap binnen de verpleegkunde en je vertrouwen in mij als onderzoeker en docent heb ik altijd als steun ervaren. De soepele manier en het abstractieniveau waarmee je in overleggen meedenkt over een methodiek, het grotere kader of de menselijke relatie zullen me altijd bijblijven.

Louise, thank you for guiding me during my PhD. Your knowledge on methodology and possible structures for various designs is phenomenal. I admire your work and your drive and love your sense of humor. Thank you for all the wonderful moments in various places we have experienced and for making Ema and me your tandem-PhD's on MI-E.

Ema, our collaboration is wonderful. It was amazing how we found time during the COVID pandemic between clinical shifts, teaching and other research projects

to meet online. It is always great to speak to each other, learn new words, share our experiences and doubts, and work together. Luckily, new projects are already part of our journey!

All co-authors, thank you for your input, knowledge and willingness to collaborate. It is wonderful to work together with professionals from various settings and countries. Our collaboration made this journey a wonderful trip!

Alle artsen en verpleegkundigen op de IC, dank voor jullie enthousiasme, vragen en suggesties tijdens bijscholingen, klinische lessen of de afstudeerprojecten. En natuurlijk dank voor jullie support toen ik weer aan bed ging tijdens de COVID-pandemie en twijfelde of ik dit nog wel kon. Wat een bijzonder werk doen we samen.

De mede onderzoekers op de IC, met wie ik een scala aan onderzoekstaken heb gedaan: multicenter data verzamelen tijdens de COVID-pandemie, stickers op buisjes plakken, worstelen met R-scripts, de screendienst, samples draaien op zaterdagochtend, mijn hart even luchten of genieten van koffie en taart. Ook al voelde ik me vaak de 'oma', jullie hebben me opgenomen in jullie midden. Dank.

Mijn collega's en studenten van de HvA. Het enthousiasme waarmee jullie reageerden op de onderzoeken en projecten waar ik mee bezig was, gaven me elke keer weer nieuwe energie. We bouwen samen aan de verpleegkunde van de toekomst!

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En natuurlijk mijn vrienden, familie, ouders en zus. Dank voor het vertrouwen en de ruimte die jullie me hebben gegeven. Jullie hielpen me door de moeilijke momenten heen en herinnerden me om ook tijd vrij te maken waarin we samen konden genieten van waardevolle momenten.

Klaas, je hebt me altijd gesteund tijdens dit traject. Op momenten dat ik met stoom uit mijn oren thuiskwam, of niet meer wist hoe ik het moest doen, of toch nog 'even' moest inloggen, wist jij mij, met je humor en support, weer op de rails te krijgen. Ik ben heel erg dankbaar dat wij het leven samen mogen delen!

CURRICULUM VITAE

Willemke Stilma was born at the 4th of September 1974 in Amsterdam. During her youth, she lived in various towns and countries. In 1992 she finished her secondary school in Utrecht after which she took a gap year working and travelling in the Middle-East. These experiences motivated her to learn more about human rights. In 1993, she started to study Dutch Law in Amsterdam. She did her master thesis on criminal law and had an internship to support fringe group young people at Streetcornerwork in a sub-urb of Amsterdam.

After her Masters in Law, she did a second gap year in which she travelled and volunteered in various countries. She realized she wanted to have a job in which you can work with your hands and with people, all over the world. In 2001, she started her employer paid training to become a nurse at the Slotervaart hospital in Amsterdam. Which was followed by the education to become an Intensive Care nurse at the OLVG hospital in 2008.

During her work in the ICU, she was interested in the evidence base for the clinical nursing practice. After a first study on pain assessment in invasively ventilated patients, the OLVG supported her to start the Master Evidence Based Practice in Amsterdam in 2011. She collaborated in various research projects.

In 2015, she started to become a nurse educator at the Amsterdam University of Applies Sciences. From 2017, she combined teaching with her PhD trajectory and since 2022 she is also program coordinator of the Master Critical Care. For the future Willemke has the ambition to continue to combine education and research, when possible with clinical nursing bedside.