Hubbard D, Witts C, Wong K, Stent L, Swingwood E. Adverse effects of Mechanical Insufflation-Exsufflation in Mechanically Ventilated Patients in the Adult Intensive Care Unit - A Literature Review. *ACPRC Journal*.:2-11. doi:10.56792/NIOE5015

Critical care

Adverse effects of Mechanical Insufflation-Exsufflation in Mechanically Ventilated Patients in the Adult Intensive Care Unit - A Literature Review.

Debbie Hubbard[1], C Witts[2], K Wong[3], L Stent[4], Ema Swingwood[1,5]

[1] School of Health and Social Wellbeing, University of the West of England Bristol, [2] North Bristol NHS Trust, [3] Royal Devon University Healthcare NHS Foundation Trust, [4] Finchley Memorial Hospital, [5] University Hospitals Bristol and Western NHS Foundation Trust

Keywords: Physiotherapy, Mechanical ventilation, Critical care, Cough Assist, Airway Clearance

https://doi.org/10.56792/NIOE5015

Journal of the Association of Chartered Physiotherapists in Respiratory Care

Abstract

Introduction

Mechanical ventilation via an artificial airway can impede cough, predisposing the critically ill patient to retained secretions and an increased risk of respiratory complications. Physiotherapeutic techniques aimed at mobilising secretions and optimising airway clearance are often relied upon in this cohort. Mechanical Insufflation-Exsufflation (MI-E) is a cough augmentation device that utilises positive pressure, followed by a rapid switch to negative pressure, to simulate a cough and aid sputum clearance from proximal airways. To date, MI-E has been widely researched in the neuromuscular population, with emerging use in the critically ill. However, adverse effects associated with MI-E in intubated populations remains unknown. The aim of this review was to report on the incidence of adverse events associated with MI-E in acutely invasively ventilated critically ill patients.

Methods

An electronic search of online databases was conducted using AMED, CINAHL, Cochrane Library, EMBASE, MEDLINE, SPORTDiscuss and Web of Science. Additionally, the reference lists of relevant articles were hand searched for eligible studies. Studies including adult subjects (>18 years) who were invasively ventilated and receiving MI-E were deemed eligible for inclusion. The outcome of interest was adverse events. Studies were excluded if they were in a paediatric population, not written in English language and were editorials or conference papers. Quality was assessed using the Critical Skills Appraisal Programme tool.

Results

A total 77 citations were identified, five of which met the inclusion criteria: three randomised crossover studies, one randomised parallel-group open label trial and one case series (278 participants in total). All studies applied MI-E followed by endotracheal or tracheal suction. Insufflation and exsufflation pressures ranged from +30 to +50cmH_2O and -30 to -50cmH_2O across studies. Only two studies pre-defined an adverse event. Common reported measures included heart rate, systolic and diastolic blood pressure, and oxygen saturations. Two studies reported the occurrence of an adverse event (oxygen saturations, blood pressure and heart rate changes) but noted that changes were transient and not clinically significant. Overall, all studies concluded that MI-E was a safe intervention in this patient cohort.

Conclusion

Overall, the use of MI-E in the acutely intubated patient does not result in adverse events that are clinically significant. However, limitations to the evidence base should be acknowledged and include a lack of definition and variation in outcome measures used and small sample sizes across studies. Larger clinical trials are needed, to further evaluate the safety of MI-E on clinically important parameters that are more clearly defined.

INTRODUCTION

Mechanical ventilation (MV) is a lifesaving invasive treatment strategy for critically ill patients but is associated with an increased risk of respiratory complications. The presence of an endotracheal tube limits cough effectiveness due to the glottis being held in abduction, preventing the generation of adequate intrathoracic pressures for effective cough and airway clearance.[1] The use of sedatives diminishes the cough reflex and contributes to intensive care acquired weakness due to prolonged offloading of the respiratory muscles.[1,2] Additionally, exposure to dry gases used during MV are thought to cause airway mucosal dysfunction and consequently increased sputum load and viscosity.[3] This, along with an ineffective cough can lead to sputum retention, increasing the risk of complications such as atelectasis, ventilator-acquired pneumonia, and ultimately respiratory failure.[4,5]

Many patients who are mechanically ventilated rely on physiotherapeutic techniques to mobilise secretions and optimise airway clearance. These include strategies such as suction, manual or ventilator hyperinflation and manual assisted cough. More recently cough augmentation devices such as mechanical insufflation-exsufflation (MI-E) have also been used in the ICU setting.[6] Mechanical insufflation-exsufflation is a non-invasive technique that utilises positive and negative pressure to augment expiratory airflow that facilitates sputum mobilisation.[7] Over the past two decades there has been a growing trend for the use of MI-E in ICU and an increasing evidence base for its efficacy.[8] A substantial body of evidence exists supporting the use of MI-E in patients with neuromuscular disease[7] and emerging evidence for its use in other populations.[9] To date, studies have demonstrated improvements in sputum clearance, pulmonary mechanics (airway resistance and lung compliance) and promising results in the reduction of re-intubation rates.[4,10,11]

Despite this, MI-E is often underutilised[12-14] with several barriers described including concerns regarding safety and the risk of adverse events, particularly associated to the use of high levels of positive pressure in patients who are critically ill.[12] The physiological effects of positive pressure such as altered cardiopulmonary dynamics are recognised and well documented.[15] Targeted recruitment techniques may cause undesirable effects associated with volutrauma and barotrauma, increasing the risk of a pneumothorax.[16] Other possible complications of positive pressure may include chest and abdominal pain, haemoptysis, gastroesophageal reflux, and abdominal distention.[17] Adverse effects associated with negative pressure such as lung unit de-recruitment have also been recognised in the literature[18] but not specifically with the use of MI-E. Notwithstanding this, evidence regarding the safety of using MI-E in intubated critically ill patients is sparse.[8,14] The aim of this Literature Review is to report on the occurrence of adverse events associated with MI-E in invasively ventilated critically ill patients.

METHODS

SEARCH STRATEGY

An electronic search was performed using the following databases: AMED, CINAHL, Cochrane Library, EMBASE, MEDLINE, SPORTDiscuss and Web of Science, from database inception to January 2023, using the search terms listed in Appendix 1. Additionally, reference lists of relevant articles were hand searched for eligible studies.

SELECTION CRITERIA

Inclusion criteria included (1) primary research, (2) adult subjects (18> years) who were invasively ventilated, (3) MI-E applied in isolation or in conjunction with other treatment interventions, (4) adverse effects of MI-E as an outcome. Studies were excluded if they were in a paediatric population, not written in English language and were editorials, opinion pieces or conference papers (not original data).

STUDY SELECTION

Study selection was carried out by all five reviewers. Three were rotational band 5 physiotherapists (CW, KW and LS). One a Consultant Physiotherapist and Clinical Doctoral Research Fellow (ES) and one a Senior Lecturer in Cardiorespiratory Physiotherapy (DH). Four reviewers (CW, KW, LS and ES) independently screened study titles and abstracts of the studies retrieved from the search. Any uncertainties were reviewed in full text. All reviewers screened all remaining full text studies and assessed for eligibility. This process was repeated by the lead author (DH) to ensure accuracy.

DATA EXTRACTION

Information regarding study characteristics including participants, interventions, outcomes, and results was extracted into a table by four authors and cross checked by one author (ES) (Table 1).

QUALITY ASSESSMENT

The Critical Appraisal Skills Programme (CASP) tool was utilised by four independent reviewers to assess study quality.[19] The included studies were assessed against each question using the corresponding checklist. Results were compared and any discrepancies resolved by discussion.

DATA ANALYSIS

Descriptive statistics were used to summarise quantitative data accompanied by a narrative synthesis of findings.

RESULTS

STUDY SELECTION

The study selection process is presented in Figure 1. A total 77 studies were identified through the electronic search.

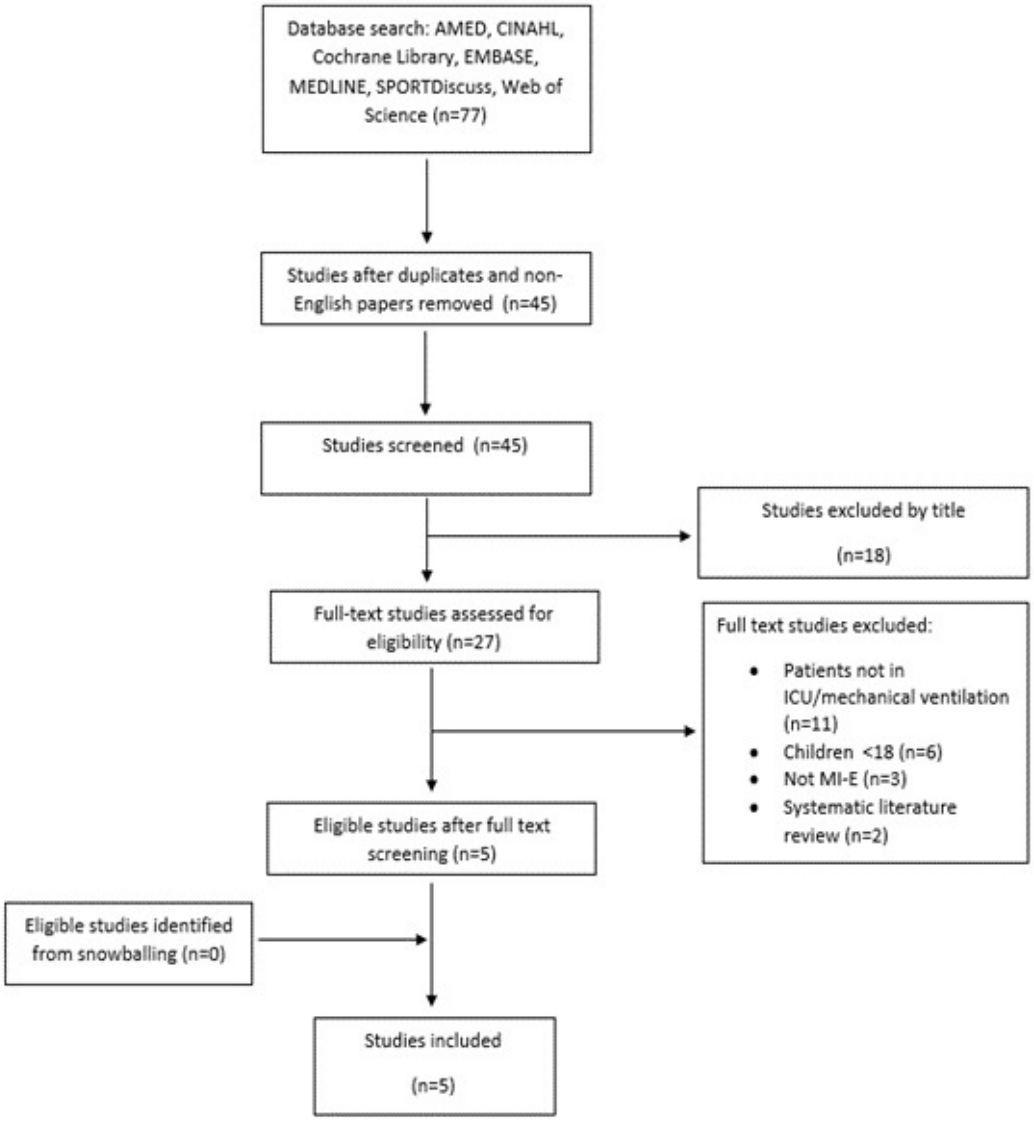

Figure 1. Flow diagram for study selection

After removal of duplicates (44) and studies not written in English (1), 45 titles were screened. A total of five studies were selected for inclusion. No further studies were identified via hand searching reference lists.

STUDY DESIGN

Of the included studies, three studies were randomised crossover studies. There was one randomised parallel-group open label trial and one case series. Studies were conducted in Brazil (n=3), France (n=1) and Spain (n=1).

STUDY CHARACTERISTICS

A summary of the included studies is shown in Table 1.

PARTICIPANTS

All studies included participants who were mechanically ventilated for more than 24 or 48 hours. Three of the five studies included participants ventilated via an ETT[10,11,20] and one study included participants with ETT and tracheostomies.[21] Participant mean age ranged from 51.4 to 75.7 years. The reason for ICU admission and diagnosis varied across studies and included surgical, medical, trauma and neurological conditions. Sample sizes ranged across studies from 13-180.

MI-E INTERVENTION

A variety of MI-E protocols were presented across included studies. All studies applied MI-E followed by ETT or tracheostomy suction. One study applied MI-E in conjunction with Expiratory Rib Cage Compressions (ERCC).[10] Coutinho et al.[22] and Sánchez-García et al.[21] provided supplementary oxygen prior to and during MI-E. One study utilised MI-E with inbuilt oscillations.[21] Mechanical insufflation-exsufflation protocols varied across studies with some lack of detail reporting. Insufflation-exsufflation pressures ranged from ±30 to ±50 cmH_2O. Insufflation and exsufflation times ranged from 2 to 3s and 1.5 to 4s respectively. Treatments

Table 1. Study characteristics.

Author	Year	Location	Study design	Study aims	Population	n	Intervention/Protocol	Outcome measures	Result
Nunes	2019	Brazil	Randomised crossover study	To evaluate effects of MI-E on respiratory mechanics haemodynamic and clearance of bronchial secretions.	Adults (>18 years) On MV > 24hrs via OTT Mixed diagnosis	16	Three protocols, 3-hr application interval: 1.MI-E (+30/-30) plus endotracheal suctioning; 2.MI-E (+50/-50) plus endotracheal suctioning; and 3.isolated endotracheal suctioning MI-E set up: Auto mode. Ti 2.5s and Te 1.5s, 0.5s pause. 4 sequences of 4 respiratory cycles and a 20 sec interval between each sequence Treatment applied by a physiotherapist.	Parameters evaluated: -5 min before -Immediately after -10 min after HR SBP DBP S_PO_2	No significant difference in HR across protocols (p=0.2) SBP and DBP significantly increased immediately after MI-E (+30/-30cmH_2O) and execution of isolated endotracheal suctioning (p=0.0006*) SpO_2 significantly reduced immediately after both the use of I/E pressures of +30/-30cmH_2O and the execution of isolated endotracheal suctioning (p=0.0001*) The execution of I/E with pressures +50/-50 cmH_2O did not result in significant changes in SBP, DBP or SpO_2.
Coutinho	2018	Brazil	Randomised crossover study	To compare the effects of MI-E verses isolated conventional tracheal suctioning on respiratory mechanics, haemodynamic stability, and aspirated secretion volume	Adults (>18 years) On MV > 48hrs Mixed diagnosis	43	Two protocols (intervention v control) Intervention: MI-E (+40/-40) 5 times in 4 cough cycles Automatic mode Ti/Te 3s, without pause. with tracheal suctioning Control - Conventional tracheal suctioning	Parameters evaluated: Before 1 min after 15 min after 30 min after HR SBP DBP MAP RR SpO_2	No significant difference over time or between groups in HR, MAP, RR and SpO_2.
Ferreira de Camillis	2018	Brazil	Randomised parallel-group, open label trail	To evaluate effectiveness of MI-E with respiratory physiotherapy v respiratory physiotherapy alone based on the weight of aspirated airway secretions	Adults (>18 years) On MV> 24hrs via ETT Medical and surgical cohort (haemodynamically stable)	180	Intervention v control Intervention: MI-E (+40/-40) 3 sets of 10 cycles Ti2s and Te3s, 2s pause, followed by orotracheal suction. Control – bilateral compression and manual vibration followed by manual hyperinflation and orotracheal suction Treatment applied by a physiotherapist	Parameters evaluated: 5 min before 5 min after WOB Ventilator adverse event 'decrease in SaO_2 by 3%' Haemodynamic adverse event 'SBP <90mmHg'	No difference in WOB between two groups No haemodynamic or ventilatory adverse events were observed
Martínez-Alejos	2021	France	Prospective single-blind randomised crossover trial	To evaluate the efficacy and safety of MI-E combined with expiratory. rib cage compressions	Adults (>18 years) On MV > 48hrs via ETT Mixed diagnosis	26	Two protocols, 4-hr washout interval: Control: ERCC followed by endotracheal suction Intervention: ERCC plus MI-E Pressures (+40/-40) 4 series of 5 I-E cycles, with a 1	Parameters evaluated: Before During After HR SBP	HR significantly increased in both treatment arms. SaO_2 significantly increased after 1hour in the ERCC+MI-E group (p=0.03*) PaO_2 significantly increased after the ERCC+MI-E intervention (p=0.003*) A total of 21 episodes of brief

Author	Year	Location	Study design	Study aims	Population	n	Intervention/Protocol	Outcome measures	Result
							min pause between series. Medium inspiratory flow I-E time 3s and 2s, 1s pause. Automatic mode Followed by endotracheal suction Treatment applied by an experienced respiratory physiotherapist.	DBP PaO_2 $PaCO_2$ SaO_2	desaturations or haemodynamic variations were documented: 10 during ERCC+MI-E 11 during ERCC (no significant difference between interventions)
Sánchez-García	2018	Spain	Case series	To evaluate the safety of MI-E use in the intubated patient population	Adults (>18 years) On MV via ETT/ tracheostomy Mixed diagnosis (Post operative, Medical Trauma)	13	MI-E with I/E pressures of +50/-45 cmH_2O, with oscillations at 16Hz Cycles of 10-12 I-E time – 3s and 4s followed by endotracheal/ tracheal suction	Parameters evaluated: At baseline Immediately before 5 min after 60 min after HR MAP SaO_2 PaO_2 $PaCO_2$ RR	No statistically significant difference in HR, MAP, $PaCO_2$ and RR between time points SaO_2 and PaO_2 significantly increased from baseline (p=0.04* and p=0.031* respectively) One episode of raised ICP (from 17cmH_2O to 28cmH_2O)

Abbreviations: **cmH_20** – centimeters of water; **DBP** – Diastolic Blood Pressure; **ERCC** – Expiratory Rib Cage Compressions; **ETT** – Endotracheal Tube; **HR** – Heart Rate; **Hrs** – Hours; **Hz** – hertz; **ICP** – Intracranial Pressure; **I/E** - Insufflation/Exsufflation; **MAP** – Mean Arterial Pressure; **MI-E** – Mechanical Insufflation-Exsufflation; **min** – minute; **MV** – Mechanical Ventilation; **OTT** – Orotracheal Tube; **$PaCO_2$** – Partial Pressure of Carbon Dioxide; **PaO_2** – Partial Pressure of Oxygen; **RR** – Respiratory Rate; **s** – second; **SaO_2** – Oxygen Saturation Level; **SBP** – Systolic Blood Pressure; **SpO_2** – Oxygen Saturation; **Ti** – Inspiratory Time; **Te** – Expiratory Time; **WOB** – Work of Breathing; * statistically significant finding

were applied by physiotherapists in three studies.[10,11,20] However, Coutinho et al.[22] and Sánchez-García et al.[21] did not detail who applied the treatment. Detail regarding clinician level of experience was not included across included studies.

OUTCOMES

Ten different outcomes across the five included studies were identified relating to safety and/or adverse events (respiratory and haemodynamic). Only two studies examined adverse events as a primary outcome.[21,22] One study provided further definition for a ventilatory and haemodynamic adverse event.[11]

OCCURRENCE OF ADVERSE EVENTS

No haemodynamic or ventilatory adverse events were observed in two of the five studies.[11,22] Of the studies that observed adverse events only transient changes were described.[10,20,21] No study reported clinically significant adverse events that required cessation of MI-E treatment or medical intervention.

DISCUSSION

The aim of this review was to report on the occurrence of adverse events associated with MI-E use in invasively ventilated critically ill patients. The findings suggest that the use of MI-E in this patient group does not result in adverse events that are clinically significant. Despite all studies concluding that MI-E is safe in this population, limitations to the evidence base should be acknowledged when interpreting the results.

There was large variation in MI-E protocols across studies and a lack of detail regarding device set up, which limits the ability to draw firm conclusions regarding the link between MI-E and adverse events. Although varied, the use of insufflation and exsufflation pressures of +40/-40cmH_2O is consistent with findings from a recent scoping review by Swingwood et al.[8] It is well documented pressures of at least +40/-40cmH_2O are required to generate higher expiratory flows.[23] However, emerging evidence suggests even higher pressures may be required in those with an artificial airway, to overcome resistance to flow.[24,25] Only one study in this review applied higher insufflation and exsufflation pressures (+50/-50 cmH_2O), which did not result in significant changes in respiratory or haemodynamic parameters.[20] This is consistent with the findings of Hyun, Lee, and Shin[25] and Martí et al.[26] where no adverse events were observed when pressures of +50/-50 cmH_2O and +40 to -70cmH_2O (respectively) were utilised. It is worth noting that Martí et al.[26] utilised pig models, therefore findings from this study cannot be extrapolated directly to a patient population. Whilst reassuring, studies investigating adverse events with higher pressures are limited.

To allow for more accurate representation of adverse events with different pressures perhaps standardisation of MI-E protocols would be preferable. Although this approach is thought to improve clinician confidence, arguably, one set protocol is unlikely to be effective and does not take into consideration individual risk factors that may predispose patients to adverse events occurring. Previously in the literature an individualised approach to MI-E set up has been advocated.[7] Progressively building up pressure until efficiency is achieved allows for careful monitoring of adverse effects and is potentially safer.

There was also a wide variation in the outcomes reported across studies including heart rate, blood pressure, oxygen saturation, respiratory rate, work of breathing and arterial blood gas measurement, which again limits comparisons. Differences in the definition of an adverse event used within studies may have caused conflicting results on their prevalence. Whilst Martínez-Alejos et al.[10] suggested a threshold for MI-E cessation (when arterial oxygen saturation falls below 85% or blood pressure changes of over 20% from baseline), only Ferreira de Camillis et al.[11] provided a clear definition for a ventilatory and haemodynamic adverse event (a decrease in oxygen saturation of 3% or drop in systolic blood pressure below 90mmHg). The remaining studies did not state at which point they determined changes in respiratory or haemodynamic parameters to be indicative of an adverse event. Therefore, the occurrence of adverse events in those studies may be under-reported. Additionally, the timepoints at which measurements were taken also varies across studies. It is worth noting that adverse events were reported as secondary outcomes in three of the five studies,[10,11,20] which again may result in the under-estimation of adverse events in this population.

Methodological quality of the included studies was assessed using the CASP tool. Overall, issues were identified relating to completeness of reporting, blinding, and a lack of pre-defined measurements. All included studies were based outside of the United Kingdom (UK) and varied in study design. Differences in ICU practices have been highlighted, in particular disparities in the management of patients who are mechanically ventilated.[27,28] Consequently, little is known about the impact of confounding factors of standard ICU care protocols. Standardisation of usual care and transparency of adjunctive interventions would mitigate potential confounders in future trials. Heterogeneity in study design limits the ability to draw comparisons across studies and make firm conclusions regarding the occurrence of adverse events with MI-E.

STRENGTHS AND LIMITATIONS OF THIS REVIEW

This review outlines the current available evidence regarding the safety of MI-E in mechanically ventilated adults. Clear inclusion and exclusion criteria were developed, and robust methodology applied. Multiple reviewers were used which was a further strength of the study methods. However, the findings of this review were limited by the paucity of studies on this topic. This review highlights that overall, there is a lack of published studies investigating the relationship between MI-E and the occurrence of adverse events, suggesting it is an under researched area. The lack of available evidence has been identified as a barrier to MI-E implementation in practice, which may be contributing

to the underutilisation of the device in this population.[13,14] The absence of robust large-scale studies is not surprising given the complexity of researching patients who are critically ill, and the ethical implications of withholding vital treatment interventions.[29] Further publication of observational studies could strengthen conclusions regarding the safety of MI-E and increase clinician confidence in the device.

CONCLUSION

There are limited studies specifically investigating whether the use of MI-E results in adverse events in critically ill patients who are mechanically ventilated. In the five studies included, MI-E was reported to be safe, and its use did not result in adverse events that are clinically significant. Variations is study design, protocols and outcome measures limit direct comparisons between studies. Therefore, further research is needed with emphasis on standardisation of protocols and usual care. Larger clinical trials are needed to further evaluate the safety of MI-E on clinically important parameters that are more clearly defined. Additionally, to improve clinician confidence in practice, further research exploring the occurrence of adverse events across a range of pressures is warranted.

Key points

- The use of MI-E in the acutely intubated patient does not result in adverse events that are clinically significant.
- There were variations in study design, MI-E protocols and outcome measures used.
- Standardisation of protocols and usual care is needed, as well as a consensus on clinically important parameters that are clearly defined.

Submitted: October 31, 2023 BST, Accepted: March 15, 2024 BST

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-4.0). View this license's legal deed at http://creativecommons.org/licenses/by/4.0 and legal code at http://creativecommons.org/licenses/by/4.0/legalcode for more information.

REFERENCES

1. McGarvey L, Rubin BK, Ebihara S, et al. Global Physiology and Pathophysiology of Cough. *Chest*. 2021;160(4):1413-1423. doi:10.1016/j.chest.2021.04.039

2. Jonkman AH, Jansen D, Heunks LMA. Novel insights in ICU-acquired respiratory muscle dysfunction: Implications for clinical care. *Crit Care*. 2017;21(1). doi:10.1186/s13054-017-1642-0

3. Lellouche F. Humidification during invasive mechanical ventilation: Hygrometric performances and cost of Humidification Systems. *Humidification in the Intensive Care Unit*. Published online September 23, 2011:137-155. doi:10.1007/978-3-642-02974-5_17

4. Gonçalves MR, Honrado T, Winck J, Paiva J. Effects of mechanical insufflation-exsufflation in preventing respiratory failure after extubation: A randomized controlled trial. *Critical Care*. 2012;16(2):R48. doi:10.1186/cc11249

5. Fernández-Carmona A, Olivencia-Peña L, Yuste-Ossorio ME, Peñas-Maldonado L. Ineffective cough and mechanical mucociliary clearance techniques. *Medicina Intensiva (Engl Ed)*. 2018;42(1):50-59. doi:10.1016/j.medin.2017.05.003

6. Tronstad O, Martí JD, Ntoumenopoulos G, Gosselink R. An update on cardiorespiratory physiotherapy during mechanical ventilation. *Semin Respir Crit Care Med*. 2022;43(03):390-404. doi:10.1055/s-0042-1744307

7. Chatwin M, Toussaint M, Gonçalves MR, et al. Airway clearance techniques in neuromuscular disorders: A state of the art review. *Respiratory Medicine*. 2018;136:98-110. doi:10.1016/j.rmed.2018.01.012

8. Swingwood EL, Stilma W, Tume LN, et al. The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults. *Respir Care*. 2022;67(8):1043-1057. doi:10.4187/respcare.09704

9. Chatwin M, Wakeman RH. Mechanical insufflation-exsufflation: Considerations for improving clinical practice. *Journal of Clinical Medicine*. 2023;12(7):2626. doi:10.3390/jcm12072626

10. Martínez-Alejos R, Martí JD, Li Bassi G, et al. Effects of mechanical insufflation-exsufflation on sputum volume in mechanically ventilated critically ill subjects. *Respir Care*. 2021;66(9):1371-1379. doi:10.4187/respcare.08641

11. Ferreira de Camillis ML, Savi A, Goulart Rosa R, et al. Effects of mechanical insufflation-exsufflation on airway mucus clearance among mechanically ventilated ICU subjects. *Respir Care*. 2018;63(12):1471-1477. doi:10.4187/respcare.06253

12. Stilma W, van der Hoeven SM, Scholte op Reimer WJM, Schultz MJ, Rose L, Paulus F. Airway care interventions for invasively ventilated critically ill adults—a Dutch National Survey. *Journal of Clinical Medicine*. 2021;10(15):3381. doi:10.3390/jcm10153381

13. Swingwood E, Stilma W, Tume L, et al. The use of mechanical insufflation-exsufflation in invasively ventilated critically ill adults: A scoping review protocol. *Syst Rev*. 2020;9(1). doi:10.1186/s13643-020-01547-8

14. Rose L, Adhikari NK, Poon J, Leasa D, McKim DA. Cough augmentation techniques in the critically ill: A Canadian national survey. *Respir Care*. 2016;61(10):1360-1368. doi:10.4187/respcare.04775

15. Mahmood SS, Pinsky MR. Heart-lung interactions during mechanical ventilation: The basics. *Ann Transl Med*. 2018;6(18):349-349. doi:10.21037/atm.2018.04.29

16. Soni N, Williams P. Positive pressure ventilation: What is the real cost? *British Journal of Anaesthesia*. 2008;101(4):446-457. doi:10.1093/bja/aen240

17. Auger C, Hernando V, Galmiche H. Use of mechanical insufflation-exsufflation devices for airway clearance in subjects with neuromuscular disease. *Respir Care*. 2017;62(2):236-245. doi:10.4187/respcare.04877

18. Park HY, Ha SY, Lee SH, et al. Repeated derecruitments accentuate lung injury during mechanical ventilation*. *Critical Care Medicine*. 2013;41(12):e423-e430. doi:10.1097/ccm.0b013e3182986268

19. CASP checklists - critical appraisal skills programme. Published 2021. https://casp-uk.net/casp-tools-checklists/

20. Nunes L de C, Rizzetti DA, Neves D, et al. Mechanical insufflation/exsufflation improves respiratory mechanics in critical care: Randomized crossover trial. *Respiratory Physiology & Neurobiology*. 2019;266:115-120. doi:10.1016/j.resp.2019.05.008

21. Sánchez-García M, Santos P, Rodríguez-Trigo G, et al. Preliminary experience on the safety and tolerability of mechanical "insufflation-exsufflation" in subjects with artificial airway. *Intensive Care Medicine Experimental*. 2018;6(1). doi:10.1186/s40635-018-0173-6

22. Coutinho WM, Vieira PJC, Kutchak FM, Dias AS, Rieder MM. Comparison of mechanical insufflation–exsufflation and endotracheal suctioning in mechanically ventilated patients: Effects on respiratory mechanics, hemodynamics, and volume of Secretions. *Indian Journal of Critical Care Medicine*. 2018;22(7):485-490. doi:10.4103/ijccm.ijccm_164_18

23. Volpe MS, Guimarães FS, Morais CC. Airway clearance techniques for mechanically ventilated patients: Insights for optimization. *Respir Care*. 2020;65(8):1174-1188. doi:10.4187/respcare.07904

24. Guérin C, Bourdin G, Leray V, et al. Performance of the coughassist insufflation-exsufflation device in the presence of an endotracheal tube or tracheostomy tube: A bench study. *Respir Care*. 2011;56(8):1108-1114. doi:10.4187/respcare.01121

25. Hyun SE, Lee SM, Shin HI. Peak expiratory flow during mechanical insufflation-exsufflation: Endotracheal Tube Versus Face Mask. *Respir Care*. 2021;66(12):1815-1823. doi:10.4187/respcare.09150

26. Martí JD, Martínez-Alejos R, Pilar-Diaz X, et al. Effects of mechanical insufflation-exsufflation with different pressure settings on respiratory mucus displacement during invasive ventilation. *Respir Care*. 2022;67(12):1508-1516. doi:10.4187/respcare.10173

27. Burns KEA, Rizvi L, Cook DJ, et al. Ventilator weaning and discontinuation practices for critically ill patients. *JAMA*. 2021;325(12):1173. doi:10.1001/jama.2021.2384

28. Russotto V, Myatra SN, Laffey JG, et al. Intubation practices and adverse peri-intubation events in critically ill patients from 29 countries. *Journal of American Medical Association (JAMA)*. 2021;325(12):1164. doi:10.1001/jama.2021.1727

29. Freitas dos Santos S, Almeida MP, Winck JC. Effects of mechanical insufflator-exsufflator in people with Spinal Cord Injury: A systematic review. *Physical Therapy Reviews*. 2022;28(1):18-29. doi:10.1080/10833196.2022.2141527

Appendix 1. Search terms

Search 1	"ICU" OR "intensive care unit" OR “critical care” OR “critical*” OR "intubat*" OR "mechanical* ventilat*" OR "artificial airway*" OR "ITU" OR "invasive* ventilat*"
Search 2	"Cough Assist" OR "NIPPY clearway" OR "MI-E" OR "MI:E" OR "mechanical insufflation-exsufflation" OR "CoughAssist E70" OR "CoughAssist T70" OR "mechanically assisted cough"
Search 3	"safe*" OR "impact*" OR "Adverse event*" OR "Adverse effect*" OR "Haemodynamic instability" OR "pneumothorax" OR "Hypotension" OR "Cardiovascular instability" OR "Harm*" OR "Negative effect*" OR "Negative event*" OR "Gastrointestinal reflux" OR "stomach distention" OR "abdomen distention" OR “work of breathing” OR “arrhythmia” OR “haemoptysis” OR “nausea” OR “bradycardia” OR “ tachycardia” OR “barotrauma” OR “dyspnoea” OR “dyspnea”