Effects of Mechanical Insufflation-Exsufflation on Airway Mucus Clearance Among Mechanically Ventilated ICU Subjects

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BACKGROUND: Few studies have evaluated the effects of mechanical insufflation-exsufflation (MI-E) in subjects on mechanical ventilation. Therefore, this study aimed to evaluate the effectiveness of MI-E on airway mucus clearance among mechanically ventilated ICU subjects. METHODS: A randomized, parallel-group, open-label trial was conducted between June and November 2017 in a single, mixed ICU. Adult ICU subjects receiving mechanical ventilation for > 24 h with stable ventilatory and hemodynamic status were randomized to receive either standard respiratory physiotherapy alone (control group) or respiratory physiotherapy by using an MI-E device (intervention group). The primary outcome was the weight of aspirated airway mucus after study interventions. Secondary outcomes included variation in static lung compliance (ΔC_L), airway resistance (ΔR_{aw}), work of breathing (ΔWOB) in relation to the pre-intervention period, and hemodynamic and ventilator complications during the procedures. RESULTS: There were 90 subjects in each group. The mean ± SD weight of the aspirated airway mucus was higher in the intervention group than in the control group (2.42 ± 2.32 g vs 1.35 ± 1.56 g, $P < .001$). The ΔC_L values in the intervention group were higher than those in the control group (1.76 ± 4.90 mL/cm H_2O vs −0.57 ± 4.85 mL/cm H_2O, $P = .001$). The ΔR_{aw} and ΔWOB values were similar between the groups. No hemodynamic or ventilatory complications were observed. CONCLUSIONS: Among the general ICU subjects receiving mechanical ventilation, use of an MI-E device during respiratory physiotherapy resulted in a larger amount of airway mucus clearance than respiratory physiotherapy alone. (ClinicalTrials.gov registration NCT03178565.) *Key words: mechanical ventilation; mucus clearance; ICU; respiratory physiotherapy*. [Respir Care 2018;63(12):1471–1477. © 2018 Daedalus Enterprises]

Introduction

Mechanically ventilated patients often have impaired airway mucus clearance. Endotracheal intubation precludes glottal closure, which is necessary for effective coughing.[1] Moreover, frequent administration of sedatives and analgesics for patient comfort and mechanical ventilation synchrony may difficult the appropriate airway mucus clearance.[2] Therefore, the standard care of ICU patients on mechanical ventilation includes respiratory physiotherapy combined with direct suction through the endotracheal tube, which aims to prevent the complications associated with mucus retention, such as pulmonary atelectasis, bronchospasm, tracheobronchitis, and pneu-

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monia.[3-6] However, endotracheal tube suctioning is effective in clearing only a small portion of the proximal airway, and this procedure may be insufficient to fully prevent the complications associated with the airway mucus retention.[7]

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Mechanical insufflation–exsufflation (MI-E) consists of lung insufflation with positive pressure, followed by an active negative-pressure exsufflation that creates a peak and sustained flow, which provides appropriate shear and velocity to loosen and move the secretions toward the mouth (or endotracheal tube) for expectoration or suctioning.[8] The active cough maneuver is not essential when MI-E is used in the invasive interfaces (orotracheal tube or tracheostomy) because the device can create an artificial cough, even in patients who are sedated or unconscious.[9-15] Despite the promising results of MI-E use in neuromuscular subjects,[16,17] use of MI-E in patients who are acutely critical is uncommon, although it is a safe technique, given that the inspiratory positive pressure during the insufflation can provide ventilatory support. In this sense, our study aimed to evaluate the efficacy of MI-E on airway mucus clearance among general ICU subjects receiving mechanical ventilation.

QUICK LOOK

Current knowledge

Mechanically ventilated patients often have impaired airway mucus clearance. Standard care includes respiratory physiotherapy combined with direct suctioning through the endotracheal tube. However, suctioning is effective in clearing only a small portion of the proximal airway, and this procedure may be insufficient to fully prevent the complications associated with airway mucus retention.

What this paper contributes to our knowledge

In this randomized clinical trial, mechanical insufflation-exsufflation was safe and resulted in a larger amount of airway mucus clearance than respiratory physiotherapy alone in the subjects who were critically ill.

Methods

Study Design

The present study was designed to be a randomized, parallel-group, open-label trial to evaluate the effectiveness of using an MI-E device during respiratory physiotherapy versus respiratory physiotherapy alone based on the weight of aspirated airway secretions among mechanically ventilated ICU subjects. All efficacy analyses were performed based on the intention-to-treat principle.

Subjects

All patients ages ≥18 y admitted to the ICU and who were ventilated ≥24 h, with stable ventilator and hemodynamic status (PEEP ≤ 8 cm H_2O, F_{IO_2} ≤ 0.40, ratio of P_{aO_2} to F_{IO_2} ≥ 150, breathing frequency ≤ 35 breaths/min, heart rate ≤ 130 beats/min, and systolic blood pressure between 90 and 160 mm Hg or diastolic blood pressure between 50 and 110 mm Hg), were included in the study. The eligibility criteria were evaluated 24 h after mechanical ventilation initiation. In some subjects, the reason for initiating mechanical ventilation was hemodynamic instability, but these subjects were included in the study only if they had recovered their normal hemodynamic status. Exclusion criteria were patients with primary neuromuscular diseases, patients in exclusive palliative treatment, and patients with pneumothorax without chest drainage or subcutaneous emphysema, which are contraindications for MI-E use.

Randomization

All the subjects were randomized on the same day that they completed mechanical ventilation for 24 h. The study group assignment was generated by using computerized randomization in blocks of different sizes. We used sequentially numbered sealed opaque envelopes for the allocated treatment regimen of the subjects to guarantee allocation concealment.

Interventions

The subjects who were randomized to the intervention group were placed in a supine position; 3 sets of 10 cycles of MI-E were performed, with pressures of −40 cm H_2O and 40 cm H_2O for insufflation and exsufflation, respectively. MI-E was performed with an inspiratory and expiratory time of 2 s and 3 s, respectively, followed by a 2-s pause between each respiratory cycle. During the study planning, we intended to use 8 cycles of MI-E.[9] However, after using the MI-E device in our practice (before starting the study recruitment), we perceived that, after these 8 cycles, there was still some amount of secretions in the orotracheal tube in some subjects. For this reason, we modified the study protocol to offer 2 more MI-E cycles for all the subjects. The device was directly connected to the

orotracheal tube. Our group did not perform any other physiotherapeutic intervention. The procedure was finalized with aspiration of the orotracheal tube 5 min after the procedure ended.

The subjects in the control group underwent respiratory physiotherapy alone, compression and manual vibration maneuvers were performed for 5 min on each side of the thorax with the subject positioned in the right and left lateral decubitus positions. All interventions were performed by the same physiotherapist the day that the subject completed 24 h of mechanical ventilation. After the intervention was performed, pulmonary auscultation and verification of the ventilator curves to certify the absence of secretion in the subject, followed by manual hyperinflation with a manual resuscitator. The procedure was finalized with aspiration of the orotracheal tube 5 min after the procedure ended. This technique was previously published.[18] The postural drainage technique was not used due to the risk of development of hemodynamic instability in these subjects who were critically ill. All the subjects remained for at least 3 h without tracheal aspiration before MI-E use or respiratory physiotherapy maneuvers, and did not receive a bolus of sedation or analgesia for the intervention.

Outcomes

The primary outcome was the weight of aspirated airway secretions 5 min after the study intervention. A single measure of the weight of the aspirated airway mucus was performed by a nurse blinded to the study interventions. All aspirated secretions were directly collected from the endotracheal tube into a 9.10-g sterile flask; this flask, with the collected secretions, was weighed on a precision scale in which the dose of saline solution, when used, was subtracted. In both study groups, no tracheal aspiration or endotracheal procedure was performed within the 3-h period preceding the study interventions.

Secondary outcomes included variation (5 min before and after administration of the study intervention) of static lung compliance (ΔC_L, expressed as mL/cm H_2O), airway resistance (ΔR_{aw}, expressed as cm H_2O/L/s), work of breathing (ΔWOB, expressed as J/L), and the occurrence of adverse ventilator or hemodynamic event during the study procedures. We decided to use ΔC_L, ΔR_{aw}, and ΔWOB as secondary outcomes to evaluate the direct effect of mucus clearing on ventilatory mechanics. A ventilatory adverse event was defined as a decrease in the oxygen saturation by 3%. A hemodynamic adverse event was defined as the occurrence of systolic blood pressure <90 mm Hg.

Sample Size and Statistical Analysis

The sample size required obtaining a difference of 0.5 g (when considering a mean of 1.9 g in the control group[19]) in the amount of airway secretions aspirated between the 2 study groups for a 2-sided alpha of 0.05, and a study power of 90% was calculated to be 170 subjects. We decided to enroll 180 subjects to compensate for potential losses. Fisher exact and Wilcoxon rank-sum tests were applied as appropriate to determine whether the baseline covariates differed between the 2 study groups. The comparison of outcomes relied on the Wilcoxon rank-sum tests. All continuous variables showed an asymmetrical distribution; therefore, we performed the Wilcoxon rank-sum test. A significance level of .05 was adopted for all comparisons. No adjustment was made for multiple comparisons; therefore, the secondary outcomes and subgroup analyses should be considered exploratory. STATA version 14 (StataCorp, College Station, Texas) was used for statistical analysis.

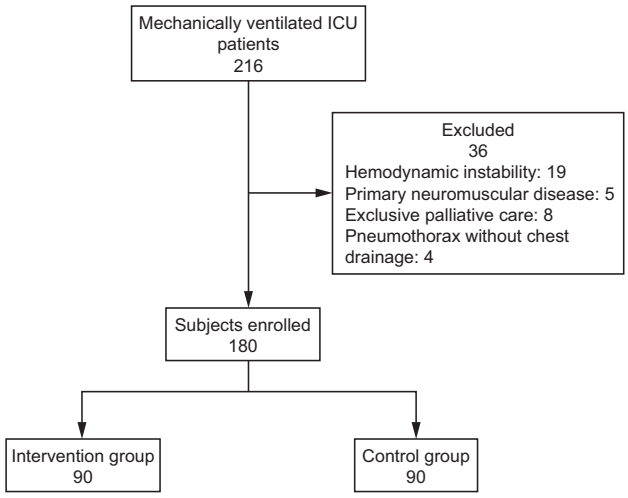

Fig. 1. Flow chart.

Ethical Issues

This study was approved by the research ethics committee at Hospital Moinhos de Vento (CAAE 55808516.5.0000.5330). Informed consent was obtained from all subjects' legally authorized representatives before study enrollment.

Results

From June to November 2017, 216 patients were screened (Fig. 1). Of these, we excluded 5 patients due to primary neuromuscular diseases, 8 due to exclusive palliative treatment, and 4 due to pneumothorax without chest drainage. We enrolled 180 subjects, with 90 subjects in each study arm. No follow-up losses occurred, and all 180 subjects were included in the intention-to-treat analysis. The baseline characteristics of the subjects are presented in Table 1. Most subjects were admitted to the ICU due to medical

Table 1. Demographic and Baseline Characteristics

Characteristic	Intervention Group ($n = 90$)	Control Group ($n = 90$)	P
Age, mean ± SD y	75.7 ± 11.1	72.7 ± 16.9	.68
Men *n* (%)	46 (51.1)	46 (51.1)	>.99
Comorbidities			
Charlson index score, mean ± SD	2.5 ± 1.9	2.8 ± 2.4	.87
COPD, *n* (%)	14 (15.5)	14 (15.5)	>.99
ICU admission type, *n* (%)			.11
Medical	63 (70.0)	73 (81.1)	
Surgical	27 (30.0)	17 (18.9)	
SAPS–3, mean ± SD	52.9 ± 13.3	54.3 ± 15.1	.54
Subjects with pneumonia, *n* (%)	31 (34.4)	28 (31.1)	.75
Reason for mechanical ventilation, *n* (%)			.32
Acute respiratory failure	36 (40.0)	44 (48.9)	
Decreased level of consciousness	20 (22.2)	24 (26.7)	
Hemodynamic instability	20 (22.2)	15 (16.6)	
Postoperative	12 (13.3)	6 (6.6)	
Cardiac arrest	2 (2.2)	1 (1.1)	
Continuous parenteral sedation, *n* (%)	53 (58.8)	54 (60.0)	>.99
Diameter of endotracheal tube, mean ± SD mm	8.0 ± 0.3	7.8 ± 1.2	.77
Mode of mechanical ventilation, *n* (%)			.63
PCV	43 (47.8)	38 (42.2)	
VCV	11 (12.2)	16 (17.8)	
PRVC	3 (3.3)	5 (5.5)	
PSV	33 (36.6)	31 (34.4)	

SAPS III = Simplified Acute Physiology Score III
PCV = pressure controlled ventilation
VCV = volume controlled ventilation
PRVC = pressure-regulated volume control ventilation
PSV = pressure support ventilation

conditions, and the most frequent reasons for mechanical ventilation, in descending order, were acute respiratory failure, decreased level of consciousness, hemodynamic instability, and cardiac arrest. All baseline variables were well balanced between the 2 study groups.

Outcomes

The mean ± SD weight of the aspirated airway secretions in the intervention group was larger than that in the control group (2.42 ± 2.32 g vs 1.35 ± 1.56 g, $P < .001$; Table 2). The ΔC_L values in the intervention group were also higher than those in the control group (1.76 ± 4.90 mL/cm H_2O vs −0.57 ± 4.85 mL/cm H_2O, $P = .001$). The mean values of ΔR_{aw} and ΔWOB did not differ between the 2 study groups. No hemodynamic or ventilatory adverse events were observed during the study interventions. The subgroup analysis for the primary outcome (Table 3) revealed that subjects ≥65 y old, subjects without COPD, and subjects admitted to the ICU due to either medical or surgical conditions benefitted from the use of the MI-E device during respiratory physiotherapy. We performed a subgroup analysis of the secondary outcomes (Table 4), and the C_L values were different for the older subjects, subjects without COPD, and subjects admitted for medical diseases.

Table 2. Primary and Secondary Outcomes

Characteristic	Intervention Group ($n = 90$)	Control Group ($n = 90$)	P
Primary outcome, mean ± SD			
Weight of aspirated secretion, g	2.42 ± 2.32	1.35 ± 1.56	<.001
Secondary outcomes, mean ± SD			
ΔC_L, mL/cm H_2O*	1.76 ± 4.90	−0.57 ± 4.85	.001
ΔR_{aw}, cm H_2O/L/s*	0 ± 3.48	0.22 ± 3.25	.59
ΔWOB, J/L	−0.03 ± 0.16	−0.03 ± 0.15	.57

* The ventilatory mode was briefly changed to constant-flow, volume-controlled ventilation for these measurements.
C_L = static lung compliance
R_{aw} = airway resistance
WOB = work of breathing

Discussion

In this single-center, randomized controlled trial performed with general adult ICU subjects on mechanical

Table 3. Subgroup Analysis of the Effects of the Use of an Insufflation-Exsufflation Device on the Mean Weight of Aspirated Airway Mucus

Variable	Intervention Group ($n = 90$)	Control Group ($n = 90$)	*P*
Age, y			
65 y	2.22 ± 0.21	1.22 ± 0.23	<.001
≥65 y	3.87 ± 0.58	1.77 ± 0.42	.050
COPD			
Yes	1.59 ± 0.52	0.87 ± 0.52	.09
No	2.57 ± 0.22	1.43 ± 0.22	<.001
ICU admission type			
Medical	2.41 ± 0.25	1.41 ± 0.23	.002
Surgical	2.44 ± 0.38	1.08 ± 0.48	.01

Data are presented as mean ± SD.

ventilation, the use of an MI-E device resulted in a larger amount of airway mucus clearance compared with respiratory physiotherapy alone. Ventilatory support is provided to patients with acute respiratory failure to provide rest for the respiratory muscles and to reduce the work of breathing until the acute condition is resolved. The mobilization and removal of respiratory secretions during physiotherapy plays an important role in improving bronchial hygiene and gas exchange, which optimizes the respiratory mechanics of patients who are critically ill and on mechanical ventilation.[7,18] Moreover, the lack of appropriate clearance of airway mucus is associated with an increased risk of adverse events, such as ventilator-associated pneumonia[5,20] and extubation failure.[7,9,21]

In the present study, we were able to reveal the effectiveness of the MI-E technique for removing airway secretions of the subjects who were critically ill and on mechanical ventilation by obtaining more than twice the clearance of airway mucus compared with the conventional respiratory physiotherapy technique. By improving this surrogate outcome, we believed that the use of MI-E during the physiotherapy of critically ill mechanically ventilated patients had the potential to improve relevant outcomes, such as ventilator-associated pneumonia, duration of mechanical ventilation, and ICU length of stay.

Cough augmentation techniques, such as lung volume recruitment or manually and mechanically assisted cough, are used to prevent and manage respiratory complications associated with chronic conditions, in particular, neuromuscular disease,[17] patients with tracheal devices,[15] and patients who receive palliative care,[4] and possibly may improve the short- and long-term outcomes for patients with acute respiratory failure.[10,22-24] Nevertheless, a Canadian survey reported that there is a moderate adoption of cough augmentation techniques, and a lack of expertise and knowledge are the potentially modifiable barriers addressed with educational interventions.[22]

Table 4. Subgroup Analysis of the Effects of the Use of an Insufflation-Exsufflation Device on Secondary Outcomes

Variable	Intervention Group ($n = 90$)	Control Group ($n = 90$)	*P*
Age			
≥65 y			
ΔC_L, mL/cm H_2O	1.70 ± 4.84	−1.01 ± 4.43	.001
ΔR_{aw}, cm H_2O/L/s	0.22 ± 3.41	0.40 ± 3.00	.99
ΔWOB, J/L	−0.02 ± 0.11	0 ± 0.09	.66
<65 y			
ΔC_L, mL/cm H_2O	2.18 ± 5.79	0.95 ± 5.96	.37
ΔR_{aw}, cm H_2O/L/s	−1.63 ± 3.69	−0.38 ± 3.99	.19
ΔWOB, J/L	−0.14 ± 0.32	−0.14 ± 0.24	.28
COPD			
Yes			
ΔC_L, mL/cm H_2O	1.50 ± 1.74	0.14 ± 2.07	.060
ΔR_{aw}, cm H_2O/L/s	−1.57 ± 4.78	0.50 ± 1.99	.38
ΔWOB, J/L	−0.07 ± 0.22	0.01 ± 0.09	.56
No			
ΔC_L, mL/cm H_2O	1.81 ± 5.32	−0.70 ± 5.20	.006
ΔR_{aw}, cm H_2O/L/s	0.28 ± 3.14	0.17 ± 3.44	.82
ΔWOB, J/L	−0.03 ± 0.14	−0.04 ± 0.16	.36
ICU admission type			
Medical			
ΔC_L, mL/cm H_2O	2.60 ± 5.35	−0.41 ± 5.23	<.001
ΔR_{aw}, cm H_2O/L/s	0.12 ± 3.92	0.15 ± 3.49	.92
ΔWOB, J/L	−0.05 ± 0.18	−0.03 ± 0.15	.68
Surgical			
ΔC_L, mL/cm H_2O	−0.18 ± 3.07	−1.23 ± 2.68	.20
ΔR_{aw}, cm H_2O/L/s	−0.29 ± 2.16	0.52 ± 1.97	.13
ΔWOB, J/L	0 ± 0.06	0 ± 0.17	.99

Data are presented as mean ± SD.
C_L = static lung compliance
R_{aw} = airway resistance
WOB = work of breathing

With regard to weaning from mechanical ventilation, Rose et al[16] reported that cough augmentation techniques when used in critically ill mechanically ventilated subjects seemed to result in fewer adverse events; however, the quality of evidence was low. The randomized trial of Gonçalves et al[9] evaluated the use of MI-E associated with noninvasive ventilation protocol used in 75 subjects dependent on mechanical ventilation for ≥48 h after extubation (MI-E plus noninvasive ventilation [35 subjects], noninvasive ventilation alone [40 subjects]). The investigators reported that successful extubation (defined as no need for re-intubation within 48 h) was higher in the MI-E plus noninvasive ventilation group (82.9% vs 52.5%, $P < .05$). They also demonstrated a reduced re-intubation

rate (17% vs 48%, $P < .05$), with a consequent reduction in the postextubation ICU length of stay (17.8 vs 11.7 d, $P < .05$) in the group of subjects treated with MI-E plus noninvasive ventilation.

Some experts indicate that several potential problems could arise when introducing MI-E therapy in a general ICU population.[25] In patients at risk for sudden lung collapse (eg, ARDS, morbid obesity, abdominal compartment syndrome) or disconnection from mechanical ventilation, along with the application of high negative airway pressure, could result in sudden profound hypoxemia. In patients who also present with copious thick secretions, intrapulmonary percussive ventilation therapy would seem to be a more reasonable and safer therapeutic option. In this context, although no ventilator or hemodynamic complications related to MI-E use occurred in our study, we did not evaluate subjects with unstable ventilator status at the moment of study procedures, and we should be cautious when extrapolating our results to this population. In addition, our subgroup analysis was unable to reveal the benefit of MI-E among subjects with COPD and with younger (<65 y) subjects. The low power to detect a subgroup effect may explain these findings; however, future research must explore the effectiveness of MI-E in these special populations.

The main limitation of this study was that none of our evaluations included important outcomes, such as survival, duration of mechanical ventilation, or length of ICU stay. Another limitation was the application of the techniques in a heterogeneous group of the subjects who were critically ill, which did not allow any conclusions in individual diseases admitted in ICU. Also, we did not include clinical variables (breathing frequency, P_{O_2}, and S_{pO_2}) as outcomes because we focused on specific proxies of modifications of ventilator mechanics. We assume that future research directions in this area would be to determine the optimal time and pressure settings in terms of efficacy, comfort, and safety for patients in critical care; and to better understand the impact of the use of asymmetric (eg, pneumonia) and symmetric (eg, ARDS) settings.

Conclusions

Our study indicated that the use of an MI-E device during respiratory physiotherapy was safe and resulted in a larger amount of airway mucus clearance than respiratory physiotherapy alone.

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