Secretion Removal in Deeply Sedated Mechanically Ventilated Subjects – Time for Implementation!

Airway clearance in mechanically ventilated patients who are deeply sedated or unable to produce sufficient cough peak flow to eliminate pulmonary secretions is always a challenge for the multidisciplinary intensive care team. Accumulated secretions in the airways induce ventilation-perfusion mismatch, gas-exchange impairment, and deterioration of pulmonary compliance, as well as augmenting the risk of respiratory infection and prolonged mechanical ventilation.[1]

The COVID-19 pandemic is bringing renewed attention to complications related to retention of respiratory secretions in mechanically ventilated patients. Bruyneel et al[2] and Torrego et al[3] reported increased requests for bronchoscopies to investigate unexplained worsening of hypoxemia or to remove bronchial plugs in patients with COVID, much more frequently than in non-COVID patients. Moreover, patients with COVID seem to be at a higher risk for developing endotracheal tube obstruction. Wiles et al[4] reported that the event rate of endotracheal tube obstruction per 1,000 ventilator days was 5.8 (95% CI 0.0–1.3) for subjects with COVID, as compared to 2.5 (95% CI 1.3–4.4) in non-COVID subjects. The use of heat-and-moisture exchangers (replacing heated humidifiers) has been cited as a possible etiology for accumulation of thick respiratory secretions. On the other hand, Wiles et al[4] suspect that the excess of secretion/plugging is somehow related to an exuberant inflammatory response that occurs in patients with COVID-19 and ARDS. Wiles et al[4] reported equal numbers of endotracheal tube obstructions in subjects with heated humidifiers and those using heat and moisture exchangers.

We also have the impression that sudden losses of regional ventilation detected with electric impedance tomography are occurring more frequently in patients with COVID due to dislodgment of mucus plugs. Apart from the reasons for secretion retention in patients with COVID, we need to consider alternatives to bronchoscopy to treat this condition. We recently published a review on insights for optimization of airway clearance techniques for mechanically ventilated patients.[5] In this review, we emphasize that, for patients under invasive ventilation, it is always advantageous to apply an expiratory flow bias, in association or not to other airway clearance techniques, to improve secretion removal. The flow bias moves mucus by using the 2-phase gas-liquid transport mechanism and is usually expressed as the ratio or difference between the peak expiratory flow (PEF) and peak inspiratory flow (PIF). A PEF-PIF difference > 33 L/min is probably effective to move secretions toward the glottis.[6] In patients under invasive ventilation, an expiratory flow bias can be applied by using volume control continuous mandatory ventilation with square wave flow and low inspiratory flow of 20–40 L/min. It is important to ensure that a PEF-PIF difference of > 33 L/min is achieved; if it is not, reducing the inspiratory flow should be considered. Most critically ill patients with COVID-19 and ARDS, even when ventilated with low tidal volumes, will probably achieve high PEF due to low respiratory system compliance. Setting an appropriate expiratory flow bias in the prone position might be an optimal opportunity to treat respiratory secretion retention.

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An alternative to improve secretion clearance is the use of mechanical insufflation-exsufflation (MI-E), which mechanically simulates cough by abruptly applying positive and negative pressure changes to the airways. MI-E can be applied either noninvasively via a mask or mouthpiece, or invasively via a tracheostomy or endotracheal tube. This therapy was developed in the early 1950s and has been used primarily to noninvasively assist airway clearance in patients with neuromuscular weakness. However, its use in mechanically ventilated patients has been increasing in the past few years.

In this issue of the Journal, Martínez-Alejos et al[7] evaluate the safety and efficacy of MI-E after a series of expiratory rib cage compressions (ERCC) in subjects requiring invasive ventilation. In this randomized crossover trial, 26 subjects on mean invasive ventilation for > 48 h were included. MI-E was applied in automatic mode with pressures set at +40/–40 cm H_2O, medium inspiratory flow, and an inspiratory/expiratory time of 3 s and 2 s, respectively, with a 1-s pause. Subjects underwent 4 series of 5 cycles, with a 1-min pause

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between series to allow reconnection to mechanical ventilation and avoid potential oxygen desaturation.

The volume of secretions cleared was significantly higher during ERCC plus MI-E compared to ERCC alone; the difference between groups was 2.18 mL (95% CI 1.24–3.12). Oxygenation increased from baseline to 1-h post-intervention and a short-term improvement in respiratory-system compliance was observed (a gain of ~ 19 mL/cm H_2O), but this improvement was not sustained. No clinically relevant complications related to MI-E were observed, and the procedure was considered safe. Subjects included in this study did not present significant gas exchange impairment, that is, only subjects with PEEP $\leq$ 10 cm H_2O were selected, and the mean P_{aO_2}/F_{IO_2} was 244 mm Hg. Thus, the application of similar maneuvers to a sample of patients with more severe impairments of gas exchange and respiratory mechanics cannot yet be considered as safe. Another concern is that it is still unknown whether the application of negative pressure might induce pulmonary collapse in patients with severely reduced respiratory system compliance, contributing to worsening gas exchange and respiratory mechanics.

Although MI-E was always preceded by a non-standardized ERCC maneuver, which may have influenced the outcomes, it was a randomized crossover study in which the main difference between interventions was the use of a mechanically assisted cough device. Thus, the differences observed may be attributed to MI-E, bringing an interesting perspective to increase the removal of proximal secretions in patients who are deeply sedated or paralyzed. As previously mentioned, these patients are among those most likely to retain secretion because of their ineffective or absent cough.

Curiously, the study of Martínez-Alejos et al[7] also revealed an unexpected finding: an inverse correlation between PEF and secretion removal. The correlation was weak (r-square 0.17, $P = .038$) and difficult to interpret, apparently contradicting the recent literature demonstrating positive correlations between PEF and secretion removal. Also, no correlation was found between expiratory flow bias and secretion removal. One factor that might have influenced these findings is that the air flows generated during the control arm (only ERCC) were not included in the linear regression analysis. It is likely that the expiratory flow bias during ERCC alone was much lower than during MI-E plus ERCC, and if data from ERCC alone had entered the analysis, a significant correlation between removal of secretion and flow bias would have been found. Another complementary explanation is that the moderate correlation found between PIF with PEF (r-square 0.66, $P < .001$) might have somehow contaminated the results. Nevertheless, as mentioned by the authors, these results should be interpreted with caution and inferences about the effects of flow bias on secretion removal in the study of Martínez-Alejos et al[7] cannot be assumed.

After acknowledging these limitations, it is important to highlight why the use of an expiratory flow bias followed by MI-E is an interesting combination of strategies for airway clearance in deeply sedated ventilated patients. While the first technique would mobilize secretions from the small airways to the larger airways, MI-E—in sequence—would act to remove secretions from proximal airways. Moreover, the MI-E technique per se could be optimized if applied in association to an expiratory flow bias.[8] In a bench study, our group found that MI-E can be optimized if applied on manual mode to slowly shift the manual control level to the inhale position over 4–5 s.[8] This reduces PIF, resulting in a higher PEF-PIF difference and greater cephalad displacement of secretions. In this study, we also noted that secretion removal is improved by setting larger MI-E pressure differentials (eg, +40/–50 cm H_2O) rather than equal pressures. Another important consideration about pressure settings during MI-E is that the presence of an artificial airway significantly reduces PEF; the narrower the inner diameter of the artificial airway, the lower the PEF for a given expiratory pressure. It is suggested that pressures no less than +40 to +50/–40 to –50 cm H_2O should be set when using MI-E in intubated or tracheostomized patients.[9]

Besides these MI-E settings that should not be ignored in future studies, we also need more studies on the use of MI-E for mechanically ventilated patients with low levels of sedation and ineffective cough. At bedside, cough assessment can be performed via measurement of cough peak flow, which has been successfully recorded in intubated or tracheostomized patients in many studies. In these patients, cough may be stimulated by using a catheter or saline instillation or voluntarily with coaching.[10] After cough stimulation, an in-line electronic spirometer or the flow versus time curve from the ventilator display is used to record cough peak flow. Because cough peak flow values < 60 L/min are associated with poor extubation outcomes in most studies,[11,12] this threshold could be used as a reference to indicate MI-E for patients with artificial airways.[13]

Ultimately, we salute the study of Martínez-Alejos et al[7] as it adds to the literature by reassuring the potential of MI-E to minimize complications related to secretion retention.[14-16] Further, we emphasize that it is time now for randomized clinical trials that investigate the effects of these strategies on hard outcomes (eg, ventilator-free days, weaning outcome, ventilator-associated pneumonia), rather than a focus on short-term changes in the volume of secretions cleared, respiratory mechanics, and hemodynamics. We sincerely hope and encourage researchers to embrace this challenge even, if appropriate, to investigate treatment of retained secretions in patients with COVID-19.

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